Attorney Docket No. 12780/102

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANTS	:	Joan D. LEONARD et al.
SERIAL NO.	:	10/726,029
FILING DATE	:	December 2, 2003
FOR	:	VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE
EXAMINER	:	Ford
GROUP ART UNIT	:	1645
CONFIRM. NO.	:	4719

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Date: March 20, 2008

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Geneveve G. Cuaycong

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TRANSMITTAL OF APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

S I R:

Transmitted herewith for filing in the above-identified patent application is an Appeal Brief Pursuant to 37 C.F.R. § 41.37.

On August 20, 2007, a Notice of Appeal was submitted from the last decision of the Examiner contained in the Final Office Action dated March 21, 2007. The Notice of Appeal is believed to have been received by the United States Patent and Trademark Office on August 23, 2007. Applicants hereby request a five-month extension of time

for submitting the Appeal Brief, from **October 23, 2007**, up to and including **March 23, 2008**.

The Commissioner is hereby authorized to charge the following small entity fees: (i) 37 C.F.R. 41.20(b)(2) Appeal Brief fee of **$255.00**; and (ii) five-month extension fee of **$1,115.00**, in the total amount of **$1,370.00** and any other fees that may be required to Kenyon & Kenyon LLP's Deposit Account No. **11-0600**. A copy of this sheet is enclosed.

Respectfully submitted,

Dated: March 20, 2008

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Enclosures

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APPEAL BRIEF

03/25/2008 SDENBOB3 00000030 110600 10726029
01 FC:2255 1115.00 DA
02 FC:2402 255.00 DA

Real Party in Interest

The real party in interest for the present application is:

BIOMUNE COMPANY
8906 Rosehill Road
Lenexa, Kansas 66215

Biomune Company is a wholly-owned subsidiary of:

CEVA SANTE ANIMALE S.A.
96, rue de la Victoire, 75009 Paris
FRANCE

Related Appeals and Interferences

The present application is a divisional application of U.S. Patent Application Serial No. 09/708,352. An Appeal Brief was filed for U.S. Patent Application Serial No. 09/708,352 on May 22 2006. A Notification of Non-compliant Appeal Brief was issued February 5, 2008. An Amended Appeal Brief was filed on March 3, 2008 together with a Petition seeking to have the Notification of Non-compliant Appeal Brief withdrawn.

Status of Claims

Claims 21-46 and 48-61 are pending. Claims 21-46 and 48-61 are under rejection and are being appealed. Claims 1-20 and 47 have been canceled.

Status of Amendments

An Amendment under 37 C.F.R. §1.116 (an Amendment after Final) was filed August 20, 2007. The Advisory Action issued September 21, 2007 stated that the Amendment after Final had been entered for the purpose of appeal.

Summary of Claimed Subject Matter

The invention defined by independent **claim 21** is a method of immunizing bovine animals **{specification, page 8, lines 28-29}** comprising administering to bovine animals at least one inactivated or attenuated *Mycoplasma bovis* biotype **{specification, page 4, lines 8-9}**, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering **{specification, Example 5, pages 18-20 (particularly page 19, lines 20-31); Example 6, pages 20-21 (particularly page 21, lines 4-15); page 22, line 28, to page 23, line 1}**.

The invention defined by independent **claim 50** is a method for immunizing bovine animals **{specification, page 8, lines 28-29}** comprising administering to bovine animals an antigenic component from at least one inactivated or attenuated *Mycoplasma bovis* biotype **{specification, page 5, lines 20-22; page 7, lines 4-7}**, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering **{specification, Example 5, pages 18-20 (particularly page 19, lines 20-31); Example 6, pages 20-21 (particularly page 21, lines 4-15); page 22, line 28, to page 23, line 1}**.

The invention defined by independent **claim 53** is a method of immunizing bovine animals **{specification, page 8, lines 28-29}** comprising:

(a) testing samples from bovine animals for the presence of *Mycoplasma bovis* biotypes, thereby identifying specific *Mycoplasma bovis* biotypes in the samples **{specification, page 14, lines 21-26}**;

(b) preparing a vaccine by inactivating at least 10^5 cell equivalents of at least one of the *Mycoplasma bovis* biotypes identified in step (a) **{specification, page 16, line 20, to page 17, line 19}**; and

(c) administering to the bovine animals the vaccine of step (b) **{specification, page 18, line 24, to page 19, line 15}**,

whereby the bovine animals are immunized so that the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering **{specification, Example 5, pages 18-20 (particularly page 19, lines 20-31); Example 6, pages 20-21 (particularly page 21, lines 4-15); page 22, line 28, to page 23, line 1}**.

Grounds of Rejection to be Reviewed on Appeal

The following grounds of rejection are present in this appeal:

(1) Are claims 21-46 and 48-61 unpatentable under 35 U.S.C. §112, first paragraph, for lack of written description?

(2) Are claims 21-46 and 48-61 unpatentable under 35 U.S.C. §112, second paragraph, for indefiniteness?

Argument

Ground of rejection 1

Are claims 21-46 and 48-61 unpatentable under 35 U.S.C. §112, first paragraph, for lack of written description?

Claims 21-46 and 48-61 were rejected for lack of written description because of the recitation of the phrase "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering." See the Office Action issued March 21, 2007, pages 3-4:

> The claims have been amended to recite "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering." ... The specification fails to show the claim limitation "a reduction in the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering." Applicant has failed to direct the Examiner as to where in the instant specification the support for this amendment is specifically shown or implied.

The Appellants respectfully submit that this rejection is in error.

It is well settled that a written description need not describe the subject matter claimed in the same words as are used in the claims. All that is necessary is that the specification reasonably convey that the inventors had possession of the claimed subject matter (*Fiers v. Revel*, 984 F.2d 1164, 1170, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993)) or clearly allow persons of ordinary skill in the art to recognize that the applicants invented what is claimed (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19

U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991)). In particular, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims" (*Eiselstein v. Frank*, 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995)). See also *All Dental Prodx, LLC v. Advantage Dental Products, Inc.*, 309 F. 3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir., 2002) ("The failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.")

Although the exact words of the phrase at issue do not appear in the present specification, the specification describes the subject matter of the phrase at issue. The specification consistently describes the "clinical incidence" of symptoms of mastitis as being less after vaccination. See, e.g., the portions of Example 5, pages 18-20, quoted below. Thus, in the context of the present invention, the phrase at issue and the term "clinical incidence" have the same meaning.[1] See the Amendment filed December 14, 2006, page 10:

> The specification consistently uses a reduction in "incidence" to refer to a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination.

There is no question that the specification provides a written description, in fact a verbatim written description, of a reduction in "clinical incidence" following vaccination.

---

[1] The phrase at issue was added to the present claims in the Amendment dated December 14, 2006 to emphasize the meaning of the term "incidence" since that term had been interpreted in the previous Office Action in a manner inconsistent with its use in the specification and the art (see the Amendment dated December 14, 2006, pages 10-12).

See, e.g., the specification, at page 19, lines 20-22: "Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination." [underscoring added]

As is well understood in the art, "clinical" means based on actual observation of the subject. Thus, the specification uses "clinical incidence" not to refer to whether a herd has less mastitis in the biological sense. Rather, the specification uses "clinical incidence" to refer to observable (i.e., clinical) indicia or symptoms of the disease. That is precisely what the rejected claim language recites.

Since the claim phrase at issue has the same meaning as "clinical incidence," and the specification provides a written description for a reduction in "clinical incidence" following vaccination, the specification also provides a written description for the phrase at issue.

Moreover, even if the relation described above between "clinical incidence" and the phrase at issue is not considered, the specification would still provide a written description for the phrase at issue. The specification repeatedly describes the administration of the recited vaccine to bovine animals, followed by a description of such beneficial effects of the vaccine on the animals as reduction in levels of infection, lack of clinical mastitis events, and lack of confirmed cases of mastitis in vaccinated animals. The specification also states that the vaccine decreases the effect of *M. bovis* infections on milk production, weight gain, and animal health, which are further indicia or "symptoms" of mastitis.

See, e.g., Example 5, on page 18-20. In Example 5, a herd suffering from endemic mastitis infection (page 18, lines 27-28) was vaccinated. The numbers of clinical (i.e., showing symptoms) *Mycoplasma bovis* infections before and after vaccination were compared and a dramatic decrease was noted.

See page 19, lines 20-31:

> Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination. Results were as follows:
>
> Pre Vaccination Base Line Incidence:
> 155 confirmed positive clinical Mycoplasma bovis infections
>
> Post Vaccination Herd Incidence:
> 1st year following vaccination:
> 24 confirmed positive clinical Mycoplasma bovis infections
> 2nd year following vaccination:
> 1 confirmed positive clinical *Mycoplasma bovis* infection.

See also Example 6, at pages 20-21, particularly the passage at page 21, lines 4-15, which reads as follows:

> A vaccine was prepared using antigen from 3 biotypes of *M. bovis* (A, B and C) as described in Example 3 above and was used to vaccinate cattle at both Site 1 and Site 2 according to the regime described in Example 5. Vaccinations began in mid-September, 1999. The incidence of Mycoplasma mastitis was monitored by independent laboratory testing for the presence of Mycoplasma in any animal determined by farm personnel to have mastitis.
>
> Following vaccination of a significant portion of the herd at Site 1 and Site 2, the incidence of mycoplasma was greatly reduced. From January 1, 2000 to July 18, 2000, there were only 10 animals reported positive for *Mycoplasma bovis* at each site. This reduction in the incidence of *Mycoplasma* positive mastitis cows was regarded as a significant reduction by the operators of Sites 1 and 2.

This passage describes a reduction in the number of animals with *Mycoplasma bovis* infections following vaccination. This reduction was recognized by farm personnel who determined whether the animals had mastitis. Although not explicitly stated, those farm personnel must have been evaluating the animals for clinical symptoms of mastitis. Thus, this passage clearly conveys the concept of the phrase at issue. That is, the number of cows showing clinical symptoms of mastitis was less after as compared to before vaccination.

See also the specification at page 22, line 28, to page 23, line 1:

> Following the initiation of the vaccination regime for the herd in February, 2000, a veterinarian monitored the herd for the incidence of *M bovis*. The dairy reported in September 2000 that there were no confirmed cases of *Mycoplasma* in vaccinated animals, despite the continued challenge from the presence of confirmed, infected nonvaccinated animals.

Here the specification describes a reduction in "confirmed cases of *Mycoplasma*." It follows necessarily, even though not explicitly stated, that the number of cows showing clinical symptoms of mastitis decreased, since the number of cases of mastitis decreased.

See also the abstract: "These vaccines demonstrate no undesirable side effects and protect against *M. bovis* related disease, such as contagious mastitis ..." If the vaccines are protecting against contagious mastitis, they must be decreasing the numbers of cows showing clinical symptoms of mastitis. To hold otherwise is to hold, contrary to common sense, that decreasing disease does not decrease symptoms of disease.

Nevertheless, the Examiner seems to be taking this anti-common sense view. See the Advisory Action issued September 21, 2007, page 4:

> The instant specification merely discloses a *reduction of animals that do not have mastitis*. [sic. The Examiner presumably meant to say "that do have mastitis"] In other words, the specification discloses the number or percentage of animals protected from disease after they have been administered the vaccine used in the claimed method. The specification is silent to the number of animals that *have symptoms of mastitis* but do not have mastitis. [italics in original]

As best the Appellants can understand the Examiner's position, the Examiner agrees with the Appellants that the specification discloses a reduction in mastitis but does not agree that the specification discloses a reduction in symptoms of mastitis. Thus, the Examiner is taking the position that an animal can have symptoms of mastitis, even though the animal does not have mastitis. No evidence was cited to support this position and the Appellants respectfully suggest that this position is untenable.

The abstract also states: "The novel vaccines also lessen the effect of *M. bovis* infections on milk production, weight gain and animal health." Here, a reduction in several clinical symptoms (decreased milk production, lack of weight gain, and poor overall health) is described. This is reiterated at the sentence bridging pages 9 and 10, which explains that administration of the vaccines of the present invention leads to "a commercially beneficial effect that lessens the effect of *M. bovis* on milk production, weight gain or animal health."

The Appellants note that the Examiner agrees that a reduction in milk production is among the symptoms of mastitis. See the Advisory Action issued September 21, 2007, page 5: "The art recognizes symptoms of mastitis as animals with swollen udders that are low milk producers to name a few."

See also page 22, lines 20-22: "[T]he vaccinated animals performed well as measured by days to market and rate of gain, both important indicators of a calf's health and well-being."

Examples 8 and 9, at pages 22-23, describes that administration of the Appellants' vaccine leads to a decrease in cases of mastitis ("[T]here were no confirmed cases of Mycoplasma in vaccinated animals ..." (Example 8, page 22, lines 30-31); "There have been no reported clinical mastitis events in vaccinated animals." (Example 9, page 23, lines 13-14)).

The numerous passages from the specification quoted above all describe a decrease in the number or percentage of cows showing observable ill effects (i.e., clinical symptoms) from mastitis infections. The Appellants submit that these passages reasonably convey that the Appellants had possession of the subject matter of the phrase "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering." Accordingly, the specification provides a written description for that phrase.

Ground of rejection 2

Are claims 21-46 and 48-61 unpatentable under 35 U.S.C. §112, second paragraph, for indefiniteness?

Claims 21-46 and 48-61 were rejected under the second paragraph of 35 U.S.C. §112 because the phrase "whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering" was considered by the Examiner to be indefinite. See the Office Action issued March 21, 2007, at the paragraph bridging pages 4-5:

> It is unclear as to what the Applicant is referring? What clinical symptoms are reduced? Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced? A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder. [underscoring in original]

The Appellants respectfully submit that this rejection is in error.

Case law holds that a claim is indefinite only if one skilled in the art would not understand what is claimed when the claim is read in light of the specification. *See, e.g., Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986) ("A decision on whether a claim is invalid under §112, 2d ¶, requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."). Furthermore, claims are not indefinite if one skilled in the art can determine whether a particular process is within the scope of the claims. *Application of Mercier*, 515 F. 2d 1161, 1168, 185 USPQ 774, 780 (CCPA 1975).

The comments in the Office Action indicate that the use of the word "symptoms" in the phrase at issue may have prompted this rejection ("What clinical symptoms are

reduced? ... A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder.").

The Appellants submit that "symptom" is a common word with a well-understood meaning. The Appellants note that the Examiner has stated that there are art-recognized meanings of the word "symptoms." See the Advisory Action issued September 21, 2007, page 6: "The Examiner agrees that the meaning of the term "symptom" is well understood." See also page 5: "The art recognizes symptoms of mastitis as animals with swollen udders that are low milk producers to name a few."

Thus, the use of the word "symptoms" does not make the claims so ambiguous that one skilled in the art would not understand what is claimed. Moreover, as explained above in connection with the written description rejection, the specification provides many examples of what is meant by symptoms (e.g., decreased milk production, lack of weight gain, and poor overall health). A reduction in milk production is among the art-recognized symptoms of mastitis acknowledged by the Examiner in the quote from page 5 of the Advisory Action in the previous paragraph.

Given that "symptoms" has a well-understood meaning, and that the specification provides examples of symptoms, it cannot be held that the use of this word makes the claims indefinite. One skilled in the art would understand what is claimed and thus would be able to determine whether a particular process is or is not within the scope of the present claims. Determining whether the number or percentage of cows showing clinical symptoms of mastitis is reduced after immunization as compared to before immunization

could be done simply by counting cows with and without a particular symptom, before and after vaccination.

The Office Action asked: "Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced?" [underscoring in original] The answer is yes, since, as explained above in connection with the written description rejection, the meaning of incidence is the same as that of the phrase at issue here. Moreover, the specification also states that the "clinical incidence" of mastitis is reduced. That means that the observable indications of the presence of mastitis are reduced, which is an exact tautology for the claim language that the number of animals with "clinical symptoms" of mastitis is less after administration of the vaccine. The claim language is therefore virtually synonymous with the specification language.

The Office Action also commented: "A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder." The Appellants submit that such a comment is not relevant to the present claims since the present claims do not require the complete elimination of a disease or disorder. Thus, even if the Examiner is correct that the animals can still have the disease even though its clinical symptoms are reduced, that has nothing to do with the claims at issue. The claims only require a decrease in symptoms (i.e., "clinical incidence"). If the vaccine is effective in reducing the undesirable symptoms of the disease, whether the animal has the disease in its system on a biological level does not matter for this invention. The claims do not purport to address this biological question. The claims only address observable symptoms, and that is precisely what is described in numerous passages and examples in the specification.

Persons skilled in the art would have no difficulty understanding this clear and obvious meaning.

CONCLUSION

For the reasons discussed above, the Appellants respectfully request that the Board of Patent Appeals and Interferences reverse:

(1) the rejection of claims 21-46 and 48-61 under 35 U.S.C. §112, first paragraph, for lack of written description; and

(2) the rejection of claims 21-46 and 48-61 under 35 U.S.C. §112, second paragraph, for indefiniteness.

Respectfully submitted,

Dated: March 20, 2008

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Enclosures

CLAIMS APPENDIX

1-20. (canceled)

21. A method of immunizing bovine animals comprising administering to bovine animals at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

22. The method of claim 21 comprising administering at least one inactivated *Mycoplasma bovis* biotype to a plurality of cows in a herd of cows and determining that the incidence of mastitis caused by *Mycoplasma bovis* in the herd before administering was greater than the incidence of mastitis caused by *Mycoplasma bovis* in the herd after administering.

23. The method of claim 22 comprising administering at least one inactivated *Mycoplasma bovis* biotype to at least about 50% of the herd.

24. The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with an adjuvant.

25. The method of claim 24 where the adjuvant is an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; incomplete Freund's adjuvant; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; saponin; carrageenan; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed

with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; paraffin oil; or muramyl dipeptide.

26. The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with a pharmaceutically acceptable excipient.

27. The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered orally, intranasally, intratracheally, intramuscularly, intramammarily, subcutaneously, intravenously, or intradermally.

28. The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered by injection, inhalation, ingestion, or infusion.

29. The method of claim 21 where the *Mycoplasma bovis* biotype has been inactivated.

30. The method of claim 29 where the *Mycoplasma bovis* biotype has been inactivated by treatment with: formalin, azide, freeze-thawing, sonication, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal, or binary ethyleneimine.

31. The method of claim 30 where the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone.

32. The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes are administered.

33. The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are selected from the group consisting of Biotype A, Biotype B, and Biotype C.

34. The method of claim 32 where at least 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

35. The method of claim 32 where approximately 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

36. The method of claim 32 where at least approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

37. The method of claim 32 where approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

38. The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are administered separately.

39. The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes and an antigen derived from another pathogen are administered.

40. The method of claim 39 where the antigen from another pathogen is from an attenuated or inactivated virus.

41. The method of claim 39 where the antigen from another pathogen is selected from the group consisting of antigens from *Staphylococcus aureus, Pasteurella hemolytica, Pasteurella multocida, Hemophilus somnus*, Bovine Respiratory Syncytial Virus, *E. coli*, and the organism causing Infectious Bovine Rhinotrachial Disease.

42. The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

43. The method of claim 42 where the analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

44. The method of claim 43 where the analysis is by PCR fingerprinting.

45. The method of claim 44 where the PCR fingerprinting uses arbitrarily chosen primers.

46. The method of claim 44 where the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

47. (canceled)

48. The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are administered in a specific ratio.

49. The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are grown separately as pure cultures, inactivated, and combined together in equal amounts before being administered to the animal.

50. A method for immunizing bovine animals comprising administering to bovine animals an antigenic component from at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

51. The method of claim 50 where antigenic components from at least two *Mycoplasma bovis* biotypes are administered.

52. The method of claim 21 where the administering results in greater milk production, greater weight gain, or less clinical disease in the bovine animal.

53. A method of immunizing bovine animals comprising:
(a) testing samples from bovine animals for the presence of *Mycoplasma bovis* biotypes, thereby identifying specific *Mycoplasma bovis* biotypes in the samples;
(b) preparing a vaccine by inactivating at least 10^5 cell equivalents of at least one of the *Mycoplasma bovis* biotypes identified in step (a); and
(c) administering to the bovine animals the vaccine of step (b),
whereby the bovine animals are immunized so that the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

54. The method of claim 53 where the sample is milk.

55. The method of claim 53 where step (a) comprises genetic analysis of DNA or RNA from the *Mycoplasma bovis* biotypes.

56. The method of claim 55 where the genetic analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

57. The method of claim 56 where the genetic analysis is PCR fingerprinting.

58. The method of claim 21 whereby the administering does not cause unfavorable reactions.

59. The method of claim 32 whereby the administering does not cause unfavorable reactions.

60. The method of claim 29 whereby the at least one inactivated *Mycoplasma bovis* biotype has not been inactivated with formalin.

61. The method of claim 32 whereby the at least two inactivated *Mycoplasma bovis* biotypes have not been inactivated with formalin.

Evidence Appendix

The evidence relied upon, and where in the record that evidence was entered, is as follows:

(1) Amendment under 37 C.F.R. §1.116 (Amendment after Final) filed August 20, 2007

(2) Office Action issued March 21, 2007

(3) Specification, filed December 2, 2003

(4) Amendment filed December 14, 2006

(5) Advisory Action issued September 21, 2007

Related Proceedings Appendix

None

Attorney Docket No. 12780/102

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Date: August 20, 2007

Signature: Genevevé G. Cuaycong

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AMENDMENT UNDER 35 U.S.C. §1.116

Sir:

In response to the Office Action dated March 21, 2007, containing a final rejection, please consider the following remarks intended to put the claims in form for allowance and/or to simplify the issues for appeal. Enclosed herewith is a Petition for the Extension of Time and a Notice of Appeal.

08/23/2007 HVUONG1 00000042 110600 10726029
02 FC:2252 225.00 DA

Remarks

Claims 21-46 and 48-61 are pending.

The rejections under 35 U.S.C. §112

Claims 21-46 and 48-61 were rejected for lack of written description because of the recitation of the phrase "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering."

The Applicants respectfully traverse this rejection.

It is well settled that a written description need not describe the subject matter claimed in the same words as are used in the claims. All that is necessary is that the specification reasonably convey that the inventors had possession of the claimed subject matter (*Fiers v. Revel*, 984 F.2d 1164, 1170, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993)) or clearly allow persons of ordinary skill in the art to recognize that the applicants invented what is claimed (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991)). In particular, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims" (*Eiselstein v. Frank*, 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995)). See also *All Dental Prodx, LLC v. Advantage Dental Products, Inc.*, 309 F. 3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir., 2002) ("The failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.")

Although the exact words of the phrase at issue do not appear in the present specification, the specification describes the subject matter of the phrase at issue. In the

context of the present invention, the phrase at issue and the term "incidence" have the same meaning.[1] See the Amendment filed December 14, 2006, page 10:

> The specification consistently uses a reduction in "incidence" to refer to a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination.

There is no question that the specification provides a written description, in fact a verbatim written description, of the term "incidence." See, e.g., the specification, at page 19, lines 20-22: "Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination." See also page 21, lines 11-12: "Following vaccination of a significant portion of the herd at Site 1 and Site 2, the incidence of mycoplasma was greatly reduced."

Since the phrase at issue has the same meaning as "incidence," and the specification provides a written description for "incidence," the specification also provides a written description for the phrase at issue.

Moreover, even if the relation described above between "incidence" and the phrase at issue is not considered, the specification would still provide a written description for the phrase at issue. The specification repeatedly describes the administration of the recited vaccine to bovine animals, followed by a description of such beneficial effects of the vaccine as reduction in levels of infection, lack of clinical mastitis events, and lack of confirmed cases of mastitis in vaccinated animals. The specification also states that the vaccine decreases the effect of *M. bovis* infections on milk production, weight gain, and animal health.

---

[1] The phrase at issue was added to the present claims in the Amendment dated December 14, 2006 to emphasize the meaning of the term "incidence" since that term had been interpreted in the previous Office Action in a manner inconsistent with its use in the specification and the art (see the Amendment dated December 14, 2006, pages 10-12).

See, e.g., Example 5, on page 18-20. In Example 5, a herd suffering from endemic mastitis infection (page 18, lines 27-28) was vaccinated. The numbers of clinical (i.e., showing symptoms) *Mycoplasma bovis* infections before and after vaccination were compared and a dramatic decrease was noted.

See page 19, lines 20-31:

> Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination. Results were as follows:
>
> Pre Vaccination Base Line Incidence:
> 155 confirmed positive clinical Mycoplasma bovis infections
>
> Post Vaccination Herd Incidence:
> 1st year following vaccination:
> 24 confirmed positive clinical Mycoplasma bovis infections
> 2nd year following vaccination:
> 1 confirmed positive clinical *Mycoplasma bovis* infection.

See also Example 6, at pages 20-21, particularly the passage at page 21, lines 4-15, which reads as follows:

> A vaccine was prepared using antigen from 3 biotypes of *M. bovis* (A, B and C) as described in Example 3 above and was used to vaccinate cattle at both Site 1 and Site 2 according to the regime described in Example 5. Vaccinations began in mid-September, 1999. The incidence of Mycoplasma mastitis was monitored by independent laboratory testing for the presence of Mycoplasma in any animal determined by farm personnel to have mastitis.
>
> Following vaccination of a significant portion of the herd at Site 1 and Site 2, the incidence of mycoplasma was greatly reduced. From January 1, 2000 to July 18, 2000, there were only 10 animals reported positive for *Mycoplasma bovis* at each site. This reduction in the incidence of *Mycoplasma* positive mastitis cows was regarded as a significant reduction by the operators of Sites 1 and 2.

This passage describes a reduction in the number of animals with *Mycoplasma bovis* infections following vaccination. This reduction was recognized by farm personnel who determined whether the animals had mastitis. Although not explicitly stated, those farm personnel must have been evaluating the animals for clinical symptoms of mastitis. Thus, this passage clearly conveys the concept of the phrase at issue. That is, the number

of cows showing clinical symptoms of mastitis was less after as compared to before vaccination.

See also the specification at page 22, line 28, to page 23, line 1:

> Following the initiation of the vaccination regime for the herd in February, 2000, a veterinarian monitored the herd for the incidence of *M bovis*. The dairy reported in September 2000 that there were no confirmed cases of *Mycoplasma* in vaccinated animals, despite the continued challenge from the presence of confirmed, infected nonvaccinated animals.

Here the specification describes a reduction in "confirmed cases of *Mycoplasma*." It follows necessarily, even though not explicitly stated, that the number of cows showing clinical symptoms of mastitis decreased, since the number of cases of mastitis decreased.

See also the abstract: "These vaccines demonstrate no undesirable side effects and protect against *M. bovis* related disease, such as contagious mastitis ..." If the vaccines are protecting against contagious mastitis, they must be decreasing the numbers of cows showing clinical symptoms of mastitis.

The abstract also states: "The novel vaccines also lessen the effect of *M. bovis* infections on milk production, weight gain and animal health." Here, a reduction in several clinical symptoms (decreased milk production, lack of weight gain, and poor overall health) is described. This is reiterated at the sentence bridging pages 9 and 10, which explains that administration of the vaccines of the present invention leads to "a commercially beneficial effect that lessens the effect of *M. bovis* on milk production, weight gain or animal health."

See also page 22, lines 20-22: "[T]he vaccinated animals performed well as measured by days to market and rate of gain, both important indicators of a calf's health and well-being."

Examples 8 and 9, at pages 22-23, describe administration of the Applicants' vaccine leading to a decrease in cases of mastitis ("[T]here were no confirmed cases of Mycoplasma in vaccinated animals ..." (Example 8, page 22, lines 30-31); "There have

been no reported clinical mastitis events in vaccinated animals." (Example 9, page 23, lines 13-14)).

The numerous passages from the specification quoted above all describe a decrease in the number or percentage of cows showing observable ill effects (i.e., clinical symptoms) from mastitis infections. The Applicants submit that these passages reasonably convey that the Applicants had possession of the subject matter of the phrase "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering." Accordingly, the specification provides a written description for that phrase.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 21-46 and 48-61 were rejected under the second paragraph of 35 U.S.C. §112 because of the phrase "whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering."

According to the Office Action, this phrase is unclear. The Office Action stated, at the paragraph bridging pages 4-5:

> It is unclear as to what the Applicant is referring? What clinical symptoms are reduced? Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced? A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder. [underscoring in original]

The Applicants respectfully traverse this rejection.

The standard for finding a claim indefinite under the second paragraph of 35 U.S.C. §112 is very difficult to meet. A claim is indefinite only if it is "insolubly ambiguous." See *Xerox Corp. v. 3Com Corp.*, 458 F. 3d 1310, 1323, 80 U.S.P.Q. 2d 1916, 1927 (Fed. Cir. 2006):

> [W]e hold that claims 9 and 11 are "subject to construction" and are not "insolubly ambiguous." For that reason, those claims are not invalid for indefiniteness. *See Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371 (Fed.Cir.2004) (holding that a claim will not be held invalid if the "meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree").

Case law holds that a claim is indefinite only if one skilled in the art would not understand what is claimed when the claim is read in light of the specification. *See, e.g., Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986) ("A decision on whether a claim is invalid under §112, 2d ¶, requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."). Furthermore, claims are not indefinite if one skilled in the art can determine whether a particular process is within the scope of the claims. *Application of Mercier*, 185 USPQ 774, 780, 515 F. 2d 1161, 1168 (CCPA 1975).

The comments in the Office Action indicate that the use of the word "symptoms" in the phrase at issue may have prompted this rejection ("What clinical symptoms are reduced? ... A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder.").

The Applicants would like to point out that "symptom" is a common word with a well-understood meaning. Thus, its use does not make the claims so ambiguous that one skilled in the art would not understand what is claimed and its use certainly does not make the claims insolubly ambiguous. Moreover, as explained above in connection with the written description rejection, the specification provides many examples of what is meant by symptoms (e.g., decreased milk production, lack of weight gain, and poor overall health).

Given that "symptoms" has a well-understood meaning, and that the specification provides examples of symptoms, it cannot be held that the use of this word makes the claims indefinite. One skilled in the art would understand what is claimed and thus would be able to determine whether a particular process is or is not within the scope of the present claims. Determining whether the number or percentage of cows showing clinical

symptoms of mastitis is reduced after immunization as compared to before immunization could be done simply by counting cows with and without a particular symptom, before and after vaccination.

The Office Action asked: "Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced?" [underscoring in original] The answer is yes, since, as explained above in connection with the written description rejection, the meaning of incidence is the same as that of the phrase at issue here.

The Office Action also commented: "A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder." The Applicants submit that such a comment is not relevant to the present claims since the present claims do not require the complete elimination of a disease or disorder.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for June 21, 2007. Enclosed is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: August 20, 2007

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,029	12/02/2003	Joan D. Leonard	12780/102	4719

26646 7590 03/21/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,029	LEONARD ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-46 and 48-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-46 and 48-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to Applicant's amendment and remarks filed December 18, 2006. Claims 21,25, 50 and 53 have been amended. Claims 1-20 and 47 have been cancelled. Claims 21-46 and 48-61 are under examination. Applicant's declaration submitted by Dr. Leonard is acknowledged. The Declaration submitted Dr. Leonard and Applicant's remarks are sufficient to overcome the art rejections. However, Applicant's amendments to the claims necessitate new grounds of rejection.

Rejections Withdrawn

2. In view of Applicant's review and response the following rejections are withdrawn:

a) rejection of claims 21-30, 50 and 52 under 35 U.S.C. 102(b), pages 2-5, paragraph 3.

b) rejection of claims 21-31, 50 and 52 under 35 U.S.C. 103(a), pages 5-8, paragraph 4.

c) rejection of claims 21-38, 42, 50 and 52 under 35 U.S.C. 103(a), pages 8-10, paragraph 5.

d) rejection of claims 21-38, 42-45 and 48-57 under 35 U.S.C. 103(a), pages 10-11, paragraph 6.

e) rejection of claims 21-39, 42-45 and 48-57 under 35 U.S.C. 103(a), pages 11-13, paragraph 7.

f) rejection of claims 21-45 and 48-57 under 35 U.S.C. 103(a), pages 13-15, paragraph 8.

g) rejection of claim 25 under 35 U.S.C. 112, second paragraph, page 15, paragraph 9.

h) rejection of claims 21-46 and 48-61 under 35 U.S.C. 112, second paragraph, page 15, paragraph 10.

i) rejection of claims 21-46 and 48-61 under 35 U.S.C. 112, second paragraph, page 16, paragraph 11.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-46 and 48-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* The amendment filed December 18, 2006 introduces new matter into the claims.

The claims have been amended to recite, "...such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering...". 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant's amendment introduces "new matter" that is not supported by the original disclosure.

The specification fails to show the claim limitation "a reduction in the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering". Applicant has failed to direct the Examiner as to where in the instant specification the support for this amendment is specifically shown or implied. In Applicant's response and marks (filed December 18, 2006) Applicant refers to incidence as a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination. Applicant points to page 19, lines 17-31 of the specification to support this conclusion. The results on page 19 measure efficacy of the vaccine. There is no mention of symptoms of disease or the percentage of symptoms reduced. The Examiner has reviewed the instant specification and has failed to find the support for the amendment. Applicant is required to cancel the new matter in the reply to this Office Action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 21-46 and 48-61 recite "whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering...". ...". It is unclear as to what the Applicant is referring? What clinical symptoms are reduced? Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced? A symptom of a disease or disorder can be reduced

and the subject still has the disease or disorder. The Clarification and/or correction is required.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Status of Claims

6. No claims are allowed.

Conclusion

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272–1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (57') 572-8300.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
March 17, 2007

NITA MINNIFIELD
PRIMARY EXAMINER

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

UTILITY PATENT APPLICATION TRANSMITTAL LETTER UNDER 37 C.F.R. 1.53(b)	ATTORNEY DOCKET NO.: 12780/102

Address to:
Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Transmitted herewith for filing is the patent application of:

Inventor(s): **Joan D. LEONARD and Robet W. TULLY**

For: **VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE**

Enclosed are:

1. **23** sheets of specification, **2** sheets of claims, and **1** sheet of abstract.

2. **2** sheets of drawings.

3. Declaration (copy from prior application (37 CFR 1.63(d) (See 4 below).

4. Incorporation by Reference. The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under paragraph 3 above is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

5. Also enclosed:
   Preliminary Amendment — Statement under 37 C.F.R. 3.73(b)
   Return Receipt postcard — Power of Attorney

6. Continuing application information:

   This application is a divisional of U.S. Patent Application Serial No. 09/708,352 filed on November 8, 2000 which claims benefit of U.S. Patent Application Serial No. 60/164,286 filed on November 8, 1999.

7. Applicant is a small entity and is entitled to small entity status

8. The filing fee has been calculated as shown below, after entry of the

accompanying Preliminary Amendment

	NUMBER FILED		NUMBER EXTRA*	RATE ($)	FEE ($)
BASIC FEE					770.00
TOTAL CLAIMS	37	- 20	17	18.00	306.00
INDEPENDENT CLAIMS	3	- 3=	1	86.00	
MULTIPLE DEPENDENT CLAIM PRESENT				290.00	0.00
*Number extra must be zero or larger				TOTAL	1,076.00
If the applicant is a small entity under 37 C.F.R. §§ 1.9 and 1.27, then divide total fee by 2, and enter amount here.				SMALL ENTITY TOTAL	538.00

10. Please charge the required application filing fee of **$538.00** to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**.

11. The Commissioner is hereby authorized to charge payment of the following fees, associated with this communication or arising during the pendency of this application, or to credit any overpayment to the deposit account of **Kenyon & Kenyon**, deposit account number **11-0600**.

A. Any additional filing fees required under 37 C.F.R.§ 1.16;
B. Any additional patent application processing fees under 37 C.F.R. § 1.17;
C. Any additional patent issue fees under 37 C.F.R. § 1.18;
D. Any additional document supply fees under 37 C.F.R. § 1.19;
E. Any additional post-patent processing fees under 37 C.F.R. § 1.20; or
F. Any additional miscellaneous fees under 37 C.F.R. § 1.21.

12. A duplicate copy of this sheet is enclosed.

Dated: DEC. 1, 2003

By: Joseph A Coppola
Joseph A. Coppola (Reg. No. 38,413)

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VACCINES FOR *MYCOPLASMA BOVIS* AND METHODS OF USE

This application claims the benefit of priority of U.S. Provisional Application No. 60/164,286, filed November 8, 1999, the entire contents of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to novel vaccines for protection against *Mycoplasma bovis* disease in animals, compositions for the diagnosis of such infections, and methods of diagnosis and vaccination.

BACKGROUND OF THE INVENTION

Mycoplasma bovis is a pathogenic prokaryote belonging to a class of organisms that is intermediate in size between a bacteria and virus. These mycoplasmas are the smallest of the free-living microorganisms. They are characterized by the lack of a cell wall and are enveloped with only a cell membrane, which allows for varying morphological shapes and unique growth requirements.

Mycoplasmas are known to cause infectious disease in most species of animals. In bovine species, *Mycoplasma bovis* is an opportunistic microorganism that causes infectious disease that is of significant economic importance to the livestock industry. *Mycoplasma bovis* isolation in a diseased bovine can be the result of its role as either a primary or secondary causative etiological disease agent. Clinical disease and losses associated with infections caused by *Mycoplasma bovis* in beef and dairy cattle include: contagious mastitis, respiratory pneumonia, joint infections (arthritic conditions), keratoconjunctivitis, and middle ear infections. Even though several species of mycoplasmas have been isolated in cattle, by far the most prevalent is *Mycoplasma bovis*. For mastitis infections, the prevalence of *M.bovis* is reported to be 70% or more.

Diseases caused by mycoplasmas are often resistant to antimicrobial therapy, leaving no effective means of treatment. Consequently, the only effective control method is to cull animals from a herd. This has enormous economic implications in the dairy industry where losses are measured by the value of the culled animals as well as the impact on both milk quality and quantity due to clinical and subclinical infections. Mycoplasma infections resulting in bovine mastitis are increasing in prevalence and geographical distribution. In the United States, this higher prevalence is due to a larger and more intense cattle production industry in which herds are rapidly expanding, placing them at greater risk. Increased incidence of *M. bovis* infection and related infectious disease in dairy herds has been noted worldwide (Jasper, DE 1982, J. Amer. Vet. Med. Assn. 181:158-162).

Control of disease caused by mycoplasmas in swine and avian species has occurred in recent years as the result of successful vaccination programs using safe and efficacious products. The design and development of an effective commercial vaccine in the United States to control *Mycoplasma bovis* has not yet occurred, even though changes in cattle production methods and husbandry practices have resulted in a greater commercial need to control this agent from both an economic and food quality perspective. Although there have been numerous attempts to produce vaccine to protect against *Mycoplasma bovis*, the resulting experimental vaccines have been deemed unacceptable due to the lack of protection as well as unacceptable site reactions in vaccinated animals (Boothby, et al. 1986 Cornell Vet 76: 188-197; Boothby et al. 1987 Can J. Veterinary Research 51:121-125; Howard et al. 1987 Veterinary Record 121:372-376; Boothby, et al. 1988 Can J. Veterinary Research 52:355-359). Thus, there remains a need in the veterinary and animal health profession to provide a safe and effective vaccine to prevent infectious disease caused by *Mycoplasma bovis* with no unfavorable host animal reactions.

SUMMARY OF INVENTION

The invention disclosed herein provides safe and effective vaccines for the prevention of Mycoplasma bovis disease in cattle. Also disclosed are methods for characterizing biotypes of *Mycoplasma bovis* in cattle, bulk milk tanks, and barns.

DESCRIPTION OF FIGURES

Figure 1 is an illustration of the gel electrophoretic pattern for DNA products produced by Polymerase Chain Reactions from different *Mycoplasma bovis* isolates. On the left side of the figure, molecular weight standards based on restriction endonuclease digests of lambda and phi phage are shown. The size of the bands in the standard digests are, from top to bottom, for lambda; n/d, n/d, n/d, 2027, 1904, 1584, 1375, 947, 831 and 564 base pairs, and for Phi X174; 1353, 1078, 872, 603, 310, 284/271, 234, 194 and 118 base pairs. The relative location of PCR-generated markers for different biotypes, designated A and B, are shown in lanes 5-12 to the right of the standards. Arrows in lanes 5 and 7 indicate the presence of three and two characteristic bands for biotypes A and B, respectively.

Figure 2 is an illustration of the gel electrophoretic pattern for DNA products produced by Polymerase Chain Reactions from a second set of *Mycoplasma bovis* isolates. On the left side of the figure, molecular weight standards based on restriction endonuclease digests of lambda and phi phage are shown. The size of the bands in the standard digests are, from top to bottom, for lambda; n/d, n/d, n/d, 2027, 1904, 1584, 1375, 947, 831 and 564 base pairs, and for Phi X174; 1353, 1078, 872, 603 and 310 base pairs. The relative location of PCR-generated markers for different biotypes, designated A and C, are shown in lanes 5-11 to the right of the standards. Arrows in lanes 5 and 8 indicate the presence of the three and two characteristic bands for biotypes A and C, respectively.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the specification and in the claims, "a," "an" or "the" can mean one or more, depending upon the context in which it is used.

In accordance with the purposes of this invention, as embodied and broadly described herein, this invention, in one aspect, provides a vaccine composition which is protective against *Mycoplasma bovis* disease in a bovine species, comprising one or more inactivated or attenuated *Mycoplasma bovis* biotype(s) and a pharmaceutically acceptable excipient. The term "inactivated," also referred to as "killed," means that the microorganisms are treated by any of several means known to the art so that they no longer grow or reproduce, but that the microorganisms are still capable of eliciting an immune response in the target animal. Examples of inactivating agents are: formalin, azide, freeze-thaw, sonication, heat treatment, sudden pressure drop, detergent (especially non-ionic detergents), lysozyme, phenol, proteolytic enzymes, propiolactone, Thimerosal (see United States Patent 5,338,543 Fitzgerald, et al.), and binary ethyleneimine (see United States Patent 5,565,205 Petersen, et al.). In a specific embodiment, the *Mycoplasma bovis* strains used in the vaccine are inactivated with beta-propiolactone (BPL).

Alternatively, the *M. bovis* biotypes used in the vaccine can be attenuated. The term "attenuated," also referred to as "modified live," is intended to refer to a living biotype of *Mycoplasma bovis* which has been attenuated (modified) by any of a number of methods known in the art including, but not limited to, multiple serial passage, temperature sensitive attenuation, mutation, or the like such that the resultant strain is relatively non-pathogenic to a bovine species. The modified live strain should be capable of limited replication in the vaccinated animal and of inducing a protective immune response which is protective against disease caused by virulent or wild-type *Mycoplasma bovis*.

The term "pharmaceutically acceptable" means a material that is not biologically or otherwise undesirable, *i.e.*, the material may be administered to an animal along with the immunogenic material (i.e. inactivated or attenuated *M. bovis* biotypes) without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the vaccine in which it is contained. Examples of such pharmaceutically acceptable excipients include water and physiological saline (for further examples, see Arnon, R. (Ed.) *Synthetic Vaccines* I:83-92, CRC Press, Inc., Boca Raton, Florida, 1987).

The invention disclosed herein is based in part on the discovery that *Mycoplasma bovis* infections in the field comprise mixtures of biotypes. The term "biotype" means a variant of a species, i.e. a strain, that can be distinguished by one or more characteristics, such as ribosomal RNA sequence variation, DNA polymorphisms, serological typing, or toxin production (*see e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; *DNA cloning: A Practical Approach*, Volumes I and II, Glover, D.M. ed., IRL Press Limited, Oxford, 1985; Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, N.Y. (1988)).

In another aspect of this invention, to produce an effective vaccine against *Mycoplasma bovis*, the vaccine must contain antigen derived from a biotype of *Mycoplasma bovis*. Examples of specific embodiments would include vaccines containing antigen derived from *M. bovis* biotypes A, B, or C. In a further specific embodiment, the vaccine comprises antigen derived from more than one *M. bovis* biotypes (e.g., A and B, A and C, B and C, or A, B and C). In a further specific embodiment, the vaccine comprises antigen derived from one or more *M. bovis* biotypes and antigen derived from another pathogen. In a further specific embodiment, the vaccine comprises inactivated or attenuated *M. bovis* biotype A, B or C. In a further specific embodiment, the vaccine comprises at least two inactivated or attenuated *M. bovis* biotypes (e.g., A and B, A and C, B and C, or A, B and C). In a further specific embodiment, the vaccine comprises at least one inactivated or attentuated *M. bovis*

biotype with antigen derived from another pathogen. In a preferred embodiment, the vaccine comprises inactivated or attenuated *M. bovis* biotype A, as defined herein, and at least one other biotype of *M. bovis*.

It is anticipated that additional biotypes of *M. bovis* may emerge and may be isolated with continued animal production. Additional biotypes can be added to the vaccine as needed. It is a matter of routine practice to sample bulk milk tanks and blood from cows to isolate *Mycoplasma bovis* cultures. These cultures can then be biotyped according to any of several typing techniques, as listed hereinabove. Vaccines can be formulated based on the prevalence of *M. bovis* biotypes present in the environment. Autogenous vaccines, i.e. those vaccines for use on the farm where the microorganisms are isolated, can be custom-designed to contain all biotypes found on the farm, but not any other biotype. Vaccines developed for use by a mass market, i.e. those vaccines produced for general use on many different farms containing pre-selected biotypes, can also be developed, marketed and used.

In another aspect, this invention provides a vaccine comprising a single, inactivated or attenuated *Mycoplasma bovis* biotype, a pharmaceutically acceptable excipient, and a suitable adjuvant. In a specific embodiment, the vaccine contains inactivated or attenuated *M. bovis* biotypes A, B or C or any mixture thereof and may further contain antigens from other pathogens.

In a preferred embodiment, the inactivated vaccines of this invention are produced from biotypes freshly isolated from infected animals or from cryopreserved biotype cultures freshly prepared from infected animals. In a preferred embodiment, the attenuated vaccines of this invention are produced from cultures of biotypes which have been treated so as to retain a limited ability to replicate within the vaccinated animal, but which does not retain the ability to infect other animals and cause mycoplasma-related disease. The preparation and use of attenuated vaccines is well-known to practitioners of ordinary skill in the art.

The inactivated or attenuated *M. bovis* biotype(s) may be further processed to fractionate and/or standardize the antigenic mass. For example, specific biotypes might be isolated from samples and combined to form specific combinations of biotypes in specific ratios. Similarly, components from a specific inactivated or attentuated *M. bovis* biotype might be fractionated and a subset of those fractions combined with similarly fractionated components of another biotype to standardize the antigenic component of the vaccine preparation and to optimize its efficacy. In one embodiment, the antigenic components derived from a single biotype are enriched by removing non-immunogenic components from the cells of the biotype. In another embodiment, the vaccine preparations are standardized to provide a required minimum cell content per formulated dose. In a preferred embodiment, the vaccine comprising inactivated *M. bovis* biotype(s) is formulated to deliver at least 10^8 *M. bovis* cell equivalents of each biotype per dose. A complete vaccination of a bovine species comprises the administration of recommended doses. In a preferred embodiment, two such doses will be administered. In a further preferred embodiment, three such doses will be administered. In another preferred embodiment, the vaccine comprising attenuated *M. bovis* biotype(s) is formulated to deliver at least 10^5 *M. bovis* cells per biotype. It is understood by those skilled in the art that the critical value in describing a vaccination dose is the total amount of immunogen needed to elicit a protective response by the host animal to infectious disease caused by virulent or wild-type *M. bovis*. The number and volume of doses used can be varied and are determined by the practitioner based on costs and the need to avoid deleterious side effects in the animal caused by the administration. For example, the volume of one administration typically does not exceed 2-5 milliliters. The number of doses of inactivated vaccine needed in adult animals is typically one initial dose followed by 1-2 additional doses and annual revaccination. The number of doses of attenuated vaccine in adult animals is one initial dose followed by a booster. Subsequently, annual boosters are administered.

The vaccines of the present invention may further comprise antigenic material of other viruses and/or microorganisms known to be bovine pathogens, including, but not limited to, attenuated (modified-live) or inactivated viruses or microorganisms.

Such combination vaccines provide protection against a plurality of diseases to which the bovine species are exposed, including but not limited to immunogenic compositions for *Staphylococcus aureus*, *Pasteurella hemolytica*, *Pasteurella multocida*, *Hemophilus somnus*, Bovine Respiratory Syncytial Virus, Bovine Diarrhea Virus, E. coli and Infectious Bovine Rhinotrachial Disease.

In other embodiments, the vaccine of this invention further comprises a suitable adjuvant. As used herein, an "adjuvant" is a potentiator or enhancer of the immune response. The term "suitable" is meant to include any substance which can be used in combination with the vaccine immunogen (i.e. inactivated or attenuated *M. bovis* biotypes or fractions thereof) to augment the immune response, without producing adverse reactions in the vaccinated animal. Effective amounts of a specific adjuvant may be readily determined so as to optimize the potentiation effect of the adjuvant on the immune response of an animal vaccinated. In a preferred embodiment, adjuvanting of the vaccines of this invention is a 2 – stage process utilizing firstly a 2% aluminum hydroxide solution and secondly a mineral oil. In specific embodiments, suitable adjuvants can be chosen from the following group: mineral, vegetable or fish oil with water emulsions, incomplete Freund's adjuvant, *E. coli* J5, dextran sulfate, iron oxide, sodium alginate, Bacto-Adjuvant, certain synthetic polymers such as Carbopol (BF Goodrich Company, Cleveland, Ohio), poly-amino acids and co-polymers of amino acids, saponin, carrageenan, REGRESSIN (Vetrepharm, Athens, GA), AVRIDINE (N, N-dioctadecyl-N',N'-bis(2-hydroxyethyl)-propanediamine), long chain polydispersed ß (1,4) linked mannan polymers interspersed with O-acetylated groups (e.g. ACEMANNAN), deproteinized highly purified cell wall extracts derived from non-pathogenic strain of Mycobacterium species (e.g. EQUIMUNE, Vetrepharm Research Inc., Athens GA), Mannite monooleate, paraffin oil, and muramyl dipeptide.

In another aspect, this invention discloses a method for immunizing bovine animals against infectious disease caused by *Mycoplasma bovis* comprising administering to a bovine animal immunogenic amounts of inactivated or attentuated Mycoplasma bovis biotypes to elicit a protective immune response by the animal.

Preferably, the method comprises administering at least two inactivated or attenuated *Mycoplasma bovis* biotypes to elicit a protective immune response by the animal. Immunization may be performed orally, intranasally, intratracheally, intramuscularly, intramammarily, subcutaneously, intravenously, or intradermally. The vaccine containing the inactivated or attenuated *M. bovis* biotypes can be administered by injection, by inhalation, by ingestion, or by infusion. Repeated doses of the vaccine preparations, i.e. "boosters", are preferable at periodic time intervals to enhance the immune response initially or after a long period of time since the last dose. The time interval between vaccinations varies depending on the age and condition of the animal. For lactating and adult animals, the first vaccination is preferably given at the end of the lactation cycle (i.e. "dry-off"), followed by a "booster" dose 2-4 weeks later, and preferably followed by a second booster dose 2-4 weeks thereafter. Newborn calves are preferably vaccinated at birth, followed by booster doses every 3-5 weeks until the calves are 4-6 months old and annually thereafter. However, at risk or exposed stocker and feeder animals should be vaccinated more often, preferably no less than once every 6 months.

In another embodiment of the methods of this invention, the multiple *M. bovis* biotypes comprising the vaccine can be delivered in separate administrations to the animal. For example, the vaccine comprising inactivated *M. bovis* biotypes A and B can be delivered by separately administering an immunogenic amount of biotype A in one injection and an immunogenic amount of biotype B in another injection. In a further embodiment, each separately administered biotype can be administered as a combination vaccination, comprising antigenic material of other viruses and/or microorganisms known to be bovine pathogens.

The term " immunogenic amount" means an amount of an immunogen, i.e. the inactivated or attenuated *M. bovis* biotype(s) or a portion thereof, which is sufficient to induce an immune response in a vaccinated bovine species and which protects the animal against disease caused by wild-type or virulent *M. bovis* infections upon exposure thereto or which has a commercially beneficial effect that lessens the effect of

M. bovis on milk production, weight gain or animal health. In a preferred embodiment, bovine animals are immunized by administering at least approximately 10^8 *M. bovis* cell equivalents of each inactivated biotype in the vaccine. In a specific embodiment, animals are immunized by administering at least approximately 10^8 *M. bovis* biotype A cell equivalents and approximately 10^8 *M. bovis* biotype B cell equivalents, which have been inactivated, in at least two injections. In another specific embodiment, bovine animals are immunized by administering at least approximately 10^8 *M. bovis* biotype A cell equivalents, 10^8 *M. bovis* biotype B cell equivalents and approximately 10^8 *M. bovis* biotype C cell equivalents, which have been inactivated, in at least two injections.

In another preferred embodiment, bovine animals are immunized by administering at least approximately 10^5 *M. bovis* cells of each attenuated biotype in the vaccine. In a specific embodiment, bovine animals are immunized by administering at least approximately 10^5 *M bovis* biotype A attenuated cells and at least approximately 10^5 *M bovis* biotype B attenuated cells. In another specific embodiment, bovine animals are immunized by administering at least approximately 10^5 *M. bovis* biotype A cells, 10^5 *M. bovis* biotype B cells, and 10^5 *M. bovis* biotype C cells.

In another aspect, this invention discloses a method for producing a *Mycoplasma bovis* vaccine comprising contacting at least two live *Mycoplasma bovis* biotypes with an inactivating material and incorporating the inactivated *Mycoplasma bovis* biotypes into a pharmaceutically acceptable excipient with a suitable adjuvant to produce a *Mycoplasma bovis* vaccine. In a preferred method, selected Mycoplasma bovis biotypes are grown separately as pure cultures, free of contamination by viruses, bacteria or any other microbial agent, including other biotypes of *M. bovis*, to the desired cell equivalents, inactivated as described herein, and then combined in equal amounts with a pharmaceutically acceptable excipient to produce a *Mycoplasma bovis* vaccine. Alternatively, the biotypes can be grown together as a mixed culture to the desired cell equivalents, inactivated and then, optionally, combined with a pharmaceutically acceptable excipient and a suitable adjuvant to produce a *Mycoplasma bovis* vaccine.

In a further embodiment of the hereinabove disclosed method of producing a *Mycoplasma bovis* vaccine, the inactivated or attenuated *Mycoplasma bovis* biotypes are mixed with a suitable adjuvant. In a preferred method, the suitable adjuvant is an aluminum hydroxide-oil emulsion.

Selected *M. bovis* biotypes may be used as the basis for diagnostic tools to detect the presence of *M. bovis*. In one aspect of this invention, samples from cattle would be tested for the presence of antibodies specific for *M. bovis* by contacting the samples with *M. bovis* cells or antigens derived from *M. bovis*. Examples of technologies that could be adapted to such a method include, but are not limited to, RIA, ELISA and immunoblot. Examples of specific embodiments would include antigens derived from one or more *M. bovis* biotypes (e.g., A, B, C, A and B, B and C, A and C, or A, B and C). In a preferred embodiment, antigen from each of the *M. bovis* biotypes A, B and C would be utilized to test for the presence of antibodies specific for each of the *M. bovis* biotypes, thus allowing an autogenous vaccine to be administered. In another embodiment, antibodies raised against *M. bovis* biotypes or antigens derived from selected biotypes would be used to test for the presence of *M. bovis* biotypes A, B and C. Examples of specific embodiments would include antibodies reactive to antigens derived from one or more *M. bovis* biotypes (e.g., A, B, C, A and B, B and C, A and C, or A, B and C). In another embodiment, antigens derived from different biotypes would be utilized to test for the presence of antibodies specific against antigens from a given biotype.

In a further embodiment, the present invention provides an isolated *Mycoplasma bovis* biotype A, *Mycoplasma bovis* biotype B, *Mycoplasma bovis* biotype C, or any combination thereof.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

EXAMPLES

Example 1. Characterization and Typing of Field Isolates

Strains were collected from infected animals or milk tanks. Single colonies were cultured, and each culture was analyzed for cytotoxicity and for the presence of specific DNA markers by PCR fingerprinting.

PCR fingerprinting: Arbitrarily-chosen primers were selected; Primer 1 and Primer 2 below (N representing deoxyinosine and A, C, T and G representing the four naturally-occurring bases of DNA):

Primer 1: 5' NNN NCG NCG NCA TCN GGC 3'; [SEQ ID NO: 1] and

Primer 2: 5' NCG NCT TAT CNG GCC TAC 3'; [SEQ ID NO: 2]

Mycoplasma bovis DNA was isolated and amplified, using these primers, in a polymerase chain reaction (PCR) as follows: The initial cycling step was for 120 seconds at 94 °C. Denaturation was for 30 seconds at 94 °C, followed by annealing for 90 seconds at 40 °C, extension for 120 seconds at 72 °C, with a final extension for 240 seconds at 72 °C. A total of 35 cycles of amplification were used.

The resulting DNA products of the PCR were separated by non-denaturing 1.5% agarose gel electrophoresis and were visualized by staining with ethidium bromide and illuminating the gel with a UV light source. Comparison of the resultant patterns, characteristic for a given biotype, with molecular weight standards such as the EcoRI/HindIII digest of lambda phage or the HaeIII digest of phiX174 phage, electrophoresed alongside the PCR products, allows consistent and reproducible biotyping of M. bovis strains. Examples of biotyping results using this method are provided below.

Strain ID	Culture #	% Cytotoxicity	Biotype Profile
BA2580	1	95	A
	2	0	A
BA2491	1	82	A
	2	100	A
498	1	100	A
	3	91	A
4082	1	100	B
	2	91	B
	3	83	B
Tank 2-18	1	90	A
	2	100	A
	3	100	A
Tank 2-19	1	100	A
	2	20	A
	3	100	A
L-56291	1	100	A
	2	100	A
	3	86	A
L-477	1	84	C
	2	76	C
	3	90	C
L-53219	1	66	A
	2	100	A
	3	100	A

Both cytotoxic (i.e. ≥40% cytotoxic) and noncytotoxic strains are pathogenic. While the majority of isolates are homogeneously cytotoxic, a few isolates, e.g. BA2580 and Tank 2-19, are a mixture of non-cytotoxic and cytotoxic colonies. Following extensive passage in culture, all strains become noncytotoxic, while passage through calves accentuates the initial phenotype, whether non-cytotoxic or cytotoxic. The PCR fingerprints for three *M. bovis* biotypes are illustrated in Figures 1 and 2

alongside the standards formed by the EcoRI/HindIII restriction endonuclease digest of lambda phage and the HaeIII restriction endonuclease digest of phi phage. The sizes of the resultant standard fragments, in base pairs, are listed in the description of Figures 1 and 2. A blank and a positive control for the PCR fingerprinting reactions are included in lanes 3 and 4, respectively, for both Figures 1 and 2. Further description of PCR fingerprinting can be found in Artiushin et al. Int. J. Syst. Bacteriol. 46: 324-328 (1996), Fan et al. Avian Dis. 39: 729-735 (1995) and elsewhere. Other methods of biotyping mycoplasma, or other microorganisms, are well-known to the art and may also be used in the practice of the invention (*see e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; *DNA cloning: A Practical Approach*, Volumes I and II, Glover, D.M. ed., IRL Press Limited, Oxford, 1985; Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, N.Y. (1988)).

Example 2. Preparation of an Inactivated Vaccine against Biotypes of *Mycoplasma*

A Mycoplasma bovis vaccine is prepared by inactivating a selected biotype of *Mycoplasma bovis* and combining this preparation with an adjuvant.

A. Selection of *M. bovis* biotypes

Isolates of M. bovis were obtained from samples of infected milk. These isolates were then cultured using standard techniques, such as those described by Knudtson et al. Vet. Microbiol. 11: 79-91 (1986).

Selected isolates were further expanded and characterized by biotype. Cultures of isolates representative of the characteristic biotypes, as determined by PCR fingerprinting, were selected and stocks of these biotypes were preserved by combining them with a gelatin protein hydrolysate stabilizing solution and subjecting the product to cryopreservation. Pure biotype cultures were used to inoculate a controlled fermentation of the microorganism for use in producing vaccine. PCR fingerprinting of these cultures for vaccine production confirmed their purity as single biotypes.

Subsequent testing of the cryo-preserved stock(s) was performed in a USDA licensed facility according to Title 9 Code of Federal Regulations to validate purity and identity of the culture(s). Identity was determined to be *Mycoplasma bovis* by two independent laboratories when tested by indirect immunofluorescence with specific antisera to the following species:

Mycoplasma bovis
Mycoplasma californicum
Mycoplasma alkalescens
Mycoplasma canadense
Mycoplasma bovigenitalium
Mycoplasma bovirhinis
Mycoplasma arginnii
Acholeplasma laidlawii

B. Propagation of the Pure, Isolated Biotypes

Selected strains, or biotypes, identified as being pure, were propagated in a defined media and further processed to make vaccines.

Mycoplasma bovis biotypes can be propagated in a variety of different general purpose, growth-promoting, defined media that are known to those knowledgable in the art, including, but not limited to, Hayflick Media, Adler Media, and Gourlay Media. In a preferred embodiment of this invention, the propagation medium is:

Yeast Extract:	5 grams per liter
Proteose Peptone:	2 grams per liter
Mixed substrate Peptone, such as Enhancetone:	20 grams per liter
Dextrose:	2 grams per liter

Sodium Chloride:	5 grams per liter
Sodium Phosphate:	2.5 grams per liter
Glycerol:	1 gram per liter
Nutrient	
Horse Serum:	50 ml per liter
1% NAD/Cysteine:	20 ml per liter
Water:	to volume of 1000 ml

Cultures were expanded and inoculated into media at a concentration of 10^7-10^8 cfu/milliliter. Cultures were grown at a temperature between 30 and 41 °C, under normal atmospheric oxygen pressure, with the percentage of CO_2 in the environment kept between 0% and 10%. Incubation times ranged from 8 hours to 72 hours. The endpoint of incubation is determined by the time at which the cultures reach stationary phase, as measured by standard microbiological methods.

Standard microbiological methods are used to determine immunogen mass, e.g. a direct plate count procedure or a spectophotometric optical density method based upon light absorbance of the *Mycoplasma bovis* cultured cell mass.

C. Inactivation of *Mycoplasma bovis*

Beta-propiolactone (BPL) is prepared as a 10% solution (v/v) in chilled water. The chilled solution is slowly added to the *M. bovis* culture(s) with constant stirring, thereby allowing hydrolysis. This BPL solution is added in the amount of 10 milliliters per liter of *M. bovis* culture(s). The pH of the BPL-*M. bovis* suspension is maintained between 6.5 and 7.8, by adding sodium hydroxide as needed. The suspension is warmed to room temperature and continuously agitated for 24 hours. The cells are concentrated by centrifugation at 8,000g or by ultrafiltration.

D. Adjuvanting and Formulation of Vaccine

Adjuvanting and final formulation of bulk concentrated inactivated *M. bovis* cultures were done concurrently as described in following protocol:

1) Determine the final volume batch quantity desired based upon 2 milliliters per dose. Quantity of each ingredient to be added is then calculated as described in steps 2 through 5.

2) Dispense an amount of inactivated *M. bovis* cell concentrate necessary to contain a protective dose quantity sufficient for the total number of doses being formulated, based on the cell counts determined in the live culture.

3) Dilute the inactivated *M. bovis* cell concentrate with 0.85% saline solution sufficient to bring the batch to the final desired volume (following addition of adjuvant components)

4) Adjust pH to 6.0 to 6.5 using a 10 normal hydrochloric acid solution.

5) Add an amount of 2% aluminum hydroxide solution to yield a final formulated concentration of 8% to 16%; incubate for 24 hours.

6) Using 10 N sodium hydroxide solution, readjust the pH to 7.2 to 7.4

7) Emulsify mineral oil adjuvant with the diluted aluminum hydroxide-absorbed inactivated *M. bovis* cells with an amount sufficient to yield 4% to 12% in the final formulation.

Example 3. Preparation of Vaccine against *M. bovis* Biotypes A, B and C.

A *Mycoplasma bovis* vaccine was prepared containing antigen from 3 biotypes; A, B and C. The process for preparation of vaccine from line was the same as described for Example 2 above. Immunogenic components from biotypes A, B and C were combined after inactivation of selected quantities of pure cultures of each biotype.

Example 4. Preparation of Vaccine against *M. bovis* Biotypes A, B, C and *M. alkalescens*.

Five lung and ear isolations were obtained from necropsied calves. Using indirect immunofluorescence, the isolates were identified by Biomune as:

S99-0052 - M. bovis - Lung

S99-0052 - M. bovis - Ear

S99-0053 - M. bovis - Lung

S99-0053 - M. alkalescens - Lung.

Cultures were passaged 4x in Hayflicks modified liquid media with characterization and preparation of pure cultures.

Samples of cultures from isolates S99-0052 and S99-0053 were further characterized and were determined to be pure M. bovis and M. alkalescens by an independent laboratory. Identity of isolate S99-0053 as M. alkascens was confirmed by further testing.

Two groups of isolates were further characterized. Cytotoxicity cell culture bioassays and PCR fingerprinting were performed. These assays confirmed the identification of the cultures, to be used for vaccine production, to be pure M. bovis and M. alkalescens,

From the isolated Mycoplasma, a vaccine containing antigens from M. bovis biotypes A, B, C and antigens from M. alkalescens was prepared using the protocol described earlier.

Example 5. Field Trial of Vaccine against *M. bovis* Biotype A

Efficacy of an inactivated vaccine of this invention specific for *M. bovis* biotype A was determined under field conditions at a site with an endemic mycoplasma mastitis infection in the herd. An active field challenge was confirmed, based on a historical review of cull cow losses due to *M. bovis*, farm site *M. bovis* environmental isolation records, cultural isolation of *M. bovis* from clinical mastitis cases in the non-vaccinated

animals, and isolation of *M. bovis* from dairy bulk tanks. Laboratory tests confirmed the identity of these isolations.

The dosage and regime protocol for field vaccinations were as follows:

Administration: 2 milliliter dose of an oil emulsion adjuvanted *M. bovis* vaccine; subcutaneous injection in neck region

Regime: 3 doses of vaccine

For lactating cows:

1st Vaccination at Dry Off (End of Lactation Cycle)

2nd Vaccination 2 to 3 Weeks Following 1st injection

3rd Vaccination 2 to 3 Weeks Following 2nd injection

For heifers:

The 3 doses are spaced 2-4 weeks apart prior to calving. Preferably, the last dose is administered at least 10 days prior to calving and the start of the lactation cycle.

Comparative results were used to measure efficacy of the vaccine. Samples taken from all animals presenting with clinical mastitis were cultured by an independent laboratory to monitor the absence or presence of *Mycoplasma bovis* infection of the mammary gland. Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination. Results were as follows:

Pre Vaccination Base Line Incidence:

155 confirmed positive clinical *Mycoplasma bovis* infections

Post Vaccination Herd Incidence:

1st year following vaccination:

24 confirmed positive clinical *Mycoplasma bovis* infections

2nd year following vaccination:

1 confirmed positive clinical *Mycoplasma bovis* infection

No injection reactions were observed. No inflammatory udder reactions were observed.

Animals were also evaluated for serological response using serum collected from individual animals prior to and following the 2nd vaccination. A direct ELISA was performed, with the following results for selected animals:

	O.D. values	
Animal ID:	Pre-vaccination	Post-vaccination
82651	.093	.313
82759	.189	.693
61043	.135	.273
3219	.198	.586
83550	.495	1.733
9296	.289	1.553

An immune response is indicated when the post-vaccination values exceed the pre-vaccination values by at least 2 fold.

Example 6. Field Trial of Vaccine against *M. bovis* Biotypes A, B and C

In the 3rd calendar year of the trial described in Example 5, 200 replacement cows were introduced into the herd; 100 at the same site (Site 1)as for Example 5 and 100 into a second related site located in the same geographical area (Site 2). Neither subset of replacement cows were quarantined prior to being introduced to their respective groups. Within 2 months, serious problems with Mycoplasma mastitis were reported at both Sites 1 and 2 by personnel at each site.

Testing of all cows at both sites, approximately 4,000 animals altogether, revealed the presence of 22 animals infected with *M. bovis*. Initial screening of all animals was accomplished by culturing pooled milk samples (16 cows/sample). When pooled samples were identified as positive for *M. bovis* by culturing milk, all animals in positive groups were tested individually. Three independent studies confirmed isolation of "bovis species" and identification of the three different biotypes (A, B and C) of *M.*

bovis was made by PCR fingerprinting. The PCR fingerprinting was carried-out as described above in Example 1.

A vaccine was prepared using antigen from 3 biotypes of *M. bovis* (A, B and C) as described in Example 3 above and was used to vaccinate cattle at both Site 1 and Site 2 according to the regime described in Example 5. Vaccinations began in mid-September, 1999. The incidence of Mycoplasma mastitis was monitored by independent laboratory testing for the presence of Mycloplasma in any animal determined by farm personnel to have mastitis.

Following vaccination of a significant portion of the herd at Site 1 and Site 2, the incidence of mycoplasma was greatly reduced. From January 1, 2000 to July 18, 2000, there were only 10 animals reported positive for *Mycoplasma bovis* at each site. This reduction in the incidence of *Mycoplasma* positive mastitis cows was regarded as a significant reduction by the operators of Sites 1 and 2. A breakdown of the incidence during Calendar year 2000 is as follows:

	Site 1.	Site 2
Jan	1	2
Feb	1	1
March	-	3
April	3	1
May	1	2
June	1	-
July	3	-

Example 7. Field Trial of Vaccine against *M. bovis* Biotypes A, B, C and M. alkalescens.

A vaccine prepared according to Example 4 comprising antigen from M. bovis biotypes A, B, C and M. alkalescens was used to vaccinate calves at a large 17,000 head-calf raising facility. It has been determined by the site's operators that

Mycoplasma is a major respiratory problem. Sample bleedings and serological evaluation prior to initiation of the trial indicated that approximately 50% of calves received are serologically negative as determined by direct ELISA bioassay.

Calves selected for the trial were bled and identified with numbered tags on Oct 19, 1999. Serum was immediately collected. Each of the calves was given the normal treatment regime for newborn cattle arriving at the site (colostrum, etc.). In addition, the calves were vaccinated three times with 2 mL of the vaccine prepared in Example 4. Vaccine was administered approximately every 7 days for the first 3 weeks. On Nov. 22, 1999, serum samples were taken from the 36 calves remaining of the original 50. On Dec. 21, 1999, serum samples were taken from 35 of the 36 calves remaining of the original 50 (one calf could not be located).

Response to vaccination was monitored using the ELISA bioassay used earlier to determine the serological status of calves at the site prior to initiating the trial. A representative random sample of calves (16) which had been serologically negative at day zero was monitored at day zero, post 2nd vaccination and post 3rd vaccination. A 7-fold increase in the immunological response over their pre-vaccinated status was realized in the animals following the vaccination procedure. This is believed to be a significant response and the vaccine's efficacy was confirmed by the fact that the vaccinated animals performed well as measured by days to market and rate of gain, both important indicators of a calf's health and well-being.

Example 8. Field Trial of Vaccine against *M. bovis* Biotype B.

Biotype B was isolated from a 1200 cow Jersey dairy herd experiencing Mycoplasma mastitis infections in the herd. A vaccine against Biotype B was prepared as described in Example 2 and used in a manner consistent with the vaccination regime previously described. Following the initiation of the vaccination regime for the herd in February, 2000, a veterinarian monitored the herd for the incidence of *M. bovis*. The dairy reported in September 2000 that there were no confirmed cases of Mycoplasma in vaccinated animals, despite the continued challenge from the presence of confirmed,

infected nonvaccinated animals. As of September, approximately 50% of the herd had been vaccinated. No unfavorable reactions resulting from the vaccine's use have been reported.

Example 9. Field Trial of Vaccine against *M. bovis* Biotype C.

Biotype C was isolated from a cultured isolate derived from a Holstein dairy herd of approximately 400 animals. This herd had been experiencing Mycoplasma mastitis infections and had been experiencing positive bulk milk tanks for the year prior to May, 1999. In March, 1999, thirteen cows had been identified as positive for *Mycoplasma bovis* infection. A vaccine specific for biotype C was made as described in Example 2 and was used in a manner consistent with the vaccination regime previously described. The owner and herd health veterinarian monitored performance of the vaccine. There have been no reported clinical mastitis events in vaccinated animals. No unfavorable reactions in animals receiving the product have been reported.

What is claimed is:

1. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient.

2. The vaccine of claim 1, further comprising a suitable adjuvant.

3. The vaccine of claim 1, wherein the amount of each inactivated biotype is at least 10^8 *M. bovis* cell equivalents.

4. The vaccine of claim 1, wherein the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

5. The vaccine of claim 1, wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A, biotype B and Biotype C.

6. The vaccine of claim 5, wherein the amount of each selected inactivated *Mycoplasma bovis* biotype is at least 10^8 *M. bovis* cell equivalents.

7. The vaccine of claim 5, wherein the amount of each selected attenuated *Mycoplasma bovis* biotype is at least 10^5 *M. bovis* cells.

8. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least two inactivated or attenuated *Mycoplasma bovis* biotypes and a pharmaceutically acceptable excipient.

9. The vaccine of claim 8, further comprising a suitable adjuvant.

10. The vaccine of claim 8, wherein the amount of each inactivated biotype is at least 10^8 *M. bovis* cell equivalents.

11. The vaccine of claim 8, wherein the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

12. The vaccine of claim 8, wherein the *Mycoplasma bovis* biotype is selected from the group consisting of biotype A, biotype B and biotype C.

13. A method for immunizing bovine animals against clinical disease caused by *Mycoplasma bovis* comprising administering to a bovine animal immunogenic amounts of at least one inactivated or attenuated *Mycoplasma bovis* biotype to elicit a protective immune response by the animal.

14. The method of claim 13, wherein at least one of the *M. bovis* biotypes is selected from the group consisting of biotype A, biotype B and biotype C.

15. The method of claim 13, wherein the vaccine is administered by injection.

16. The method of claim 13, wherein the vaccine is administered by inhalation.

17. The method of claim 13, wherein the vaccine is administered by ingestion.

18. A method for producing a *Mycoplasma bovis* vaccine comprising contacting at least one live *Mycoplasma bovis* biotype with an inactivating material, and combining the inactivated *Mycoplasma bovis* biotype with a pharmaceutically acceptable excipient to produce a *Mycoplasma bovis* vaccine.

19. The method of claim 18, further comprising mixing said inactivated *Mycoplasma bovis* biotype with a suitable adjuvant.

20. A method for immunizing bovine animals against disease caused by *Mycoplasma bovis* comprising administering to a bovine animal the vaccine of claim 8 to elicit a protective immune response by the animal.

ABSTRACT

The invention of novel, effective vaccines against *Mycoplasma. bovis* for use in cattle is described. These vaccines demonstrate no undesirable side effects and protect against *M. bovis* related disease, such as contagious mastitis, respiratory pneumonia, joint infections, keratoconjunctivitis and middle ear infections. The novel vaccines also lessen the effect of *M. bovis* infections on milk production, weight gain and animal health. Methods of diagnosing, characterizing and treating *M. bovis* infections as specific biotypes are also disclosed. Vaccine compositions made in accordance with the invention may be either of the attenuated or inactivated variety. Vaccines may also include antigens from other pathogens so as to provide a protective immunogenic response to diseases other than those caused by *M. bovis*.

FIGURE 1

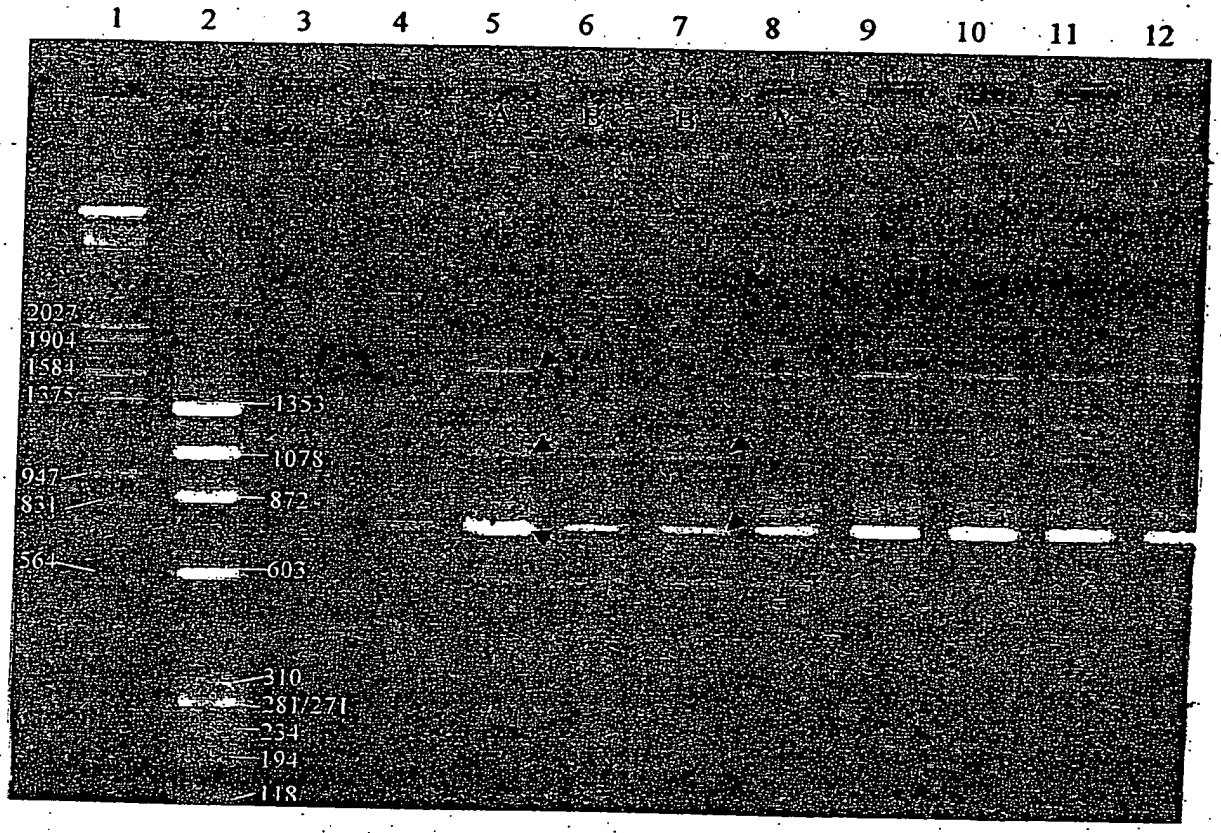
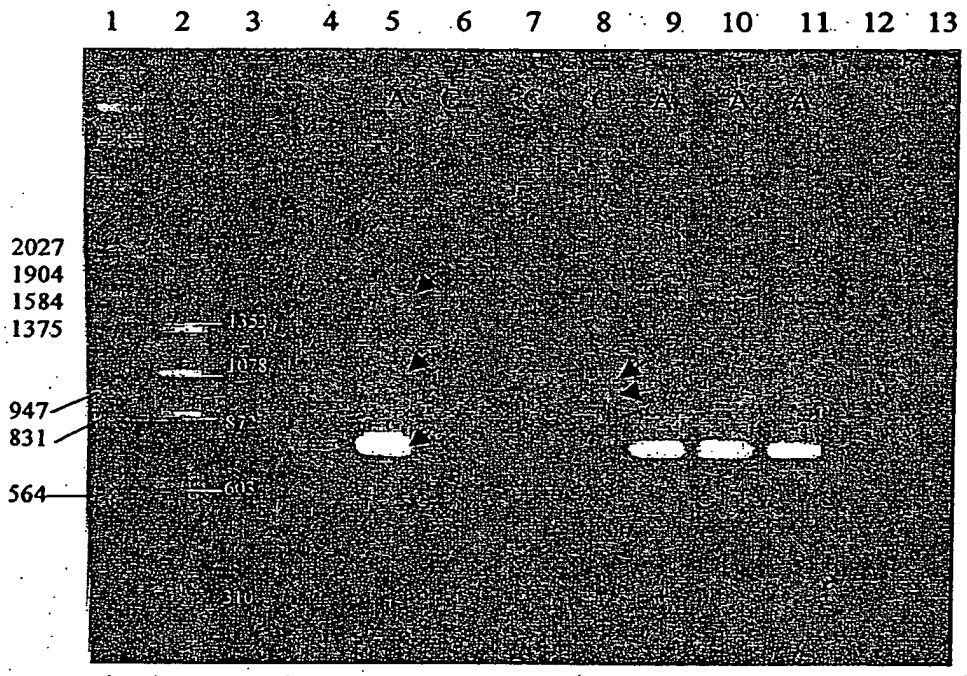


FIGURE 2



IN THE SPECIFICATION:

Page 1, line 2, after the title, please insert the following paragraph:

-- CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of prior U.S. Patent Application Serial No. 09/708,352 filed on November 8, 2002 which claims benefit of U.S. Patent Application Serial No. 60/164,286, filed on November 8, 1999, the disclosures of which are incorporated herein, in their entirety.--

Attorney Docket No. 12780/102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Joan D. LEONARD et al.
SERIAL NO.	:	Divisional of 09/708,352
FILING DATE	:	Herewith
FOR	:	VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE
EXAMINER	:	To be assigned
GROUP ART UNIT:		To be assigned

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.115

Sir:

Prior to examination on the merits, please consider the following amendments and remarks.

EV 332525 US

IN THE SPECIFICATION:

Page 1, line 2, after the title, please insert the following paragraph:

-- CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of prior U.S. Patent Application Serial No. 09/708,352 filed on November 8, 2002 which claims benefit of U.S. Patent Application Serial No. 60/164,286, filed on November 8, 1999, the disclosures of which are incorporated herein, in their entirety.--

CLAIM AMENDMENTS:

This listing of claims will replace all prior versions and listings of claims in the application:

1-20. (canceled)

21. (new) A method of immunizing bovine animals comprising administering to bovine animals at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced.

22. (new) The method of claim 21 comprising administering at least one inactivated *Mycoplasma bovis* biotype to a plurality of cows in a herd of cows and determining that the incidence of mastitis caused by *Mycoplasma bovis* in the herd before administering was greater than the incidence of mastitis caused by *Mycoplasma bovis* in the herd after administering.

23. (new) The method of claim 22 comprising administering at least one inactivated *Mycoplasma bovis* biotype to at least about 50% of the herd.

24. (new) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with an adjuvant.

25. (new) The method of claim 24 where the adjuvant is an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; incomplete Freund's adjuvant; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; saponin; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed

with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; paraffin oil; or muramyl dipeptide.

26. (new) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with a pharmaceutically acceptable excipient.

27. (new) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered orally, intranasally, intratracheally, intramuscularly, intamammarily, subcutaneously, intravenously, or intradermally.

28. (new) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered by injection, inhalation, ingestion, or infusion.

29. (new) The method of claim 21 where the *Mycoplasma bovis* biotype has been inactivated

30. (new) The method of claim 29 where the *Mycoplasma bovis* biotype has been inactivated by treatment with: formalin, azide, freeze-thawing, sonication, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal, or binary ethyleneimine.

31. (new) The method of claim 30 where the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone.

32. (new) The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes are administered.

33. (new) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are selected from the group consisting of Biotype A, Biotype B, and Biotype C.

34. (new) The method of claim 32 where at least 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

35. (new) The method of claim 32 where approximately 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

36. (new) The method of claim 32 where at least approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

37. (new) The method of claim 32 where approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

38. (new) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are administered separately.

39. (new) The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes and an antigen derived from another pathogen are administered.

40. (new) The method of claim 39 where the antigen from another pathogen is from an attenuated or inactivated virus.

41. (new) The method of claim 39 where the antigen from another pathogen is selected from the group consisting of antigens from *Staphylococcus aureus, Pasteurella hemolytica, Pasteurella multocida, Hemophilus somnus*, Bovine Respiratory Syncytial Virus, *E. coli*, and the organism causing Infectious Bovine Rhinotrachial Disease.

42. (new) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

43. (new) The method of claim 42 where the analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

44. (new) The method of claim 43 where the analysis is by PCR fingerprinting.

45. (new) The method of claim 44 where the PCR fingerprinting uses arbitrarily chosen primers.

46. (new) The method of claim 44 where the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

47. (new) The method of claim 32 where the at least two *Mycoplasma bovis* biotypes have been identified as being different biotypes by a process comprising:
(a) isolating DNA from the biotypes;
(b) amplifying the DNA by PCR;
(c) separating the amplified DNA by gel electrophoresis; and
(d) comparing the resulting patterns from the gel electrophoresis to identify the different biotypes.

48. (new) The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are administered in a specific ratio.

49. (new) The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are grown separately as pure cultures, inactivated, and combined together in equal amounts before being administered to the animal.

50. (new) A method for immunizing bovine animals comprising administering to bovine animals an antigenic component from at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced.

51. (new) The method of claim 50 where antigenic components from at least two *Mycoplasma bovis* biotypes are administered.

52. (new) The method of claim 21 where the administering results in greater milk production, greater weight gain, or less clinical disease in the bovine animal.

53. (new) A method of immunizing bovine animals comprising:
(a) testing samples from bovine animals for the presence of *Mycoplasma bovis* biotypes, thereby identifying specific *Mycoplasma bovis* biotypes in the samples;
(b) preparing a vaccine by inactivating at least 10^5 cell equivalents of at least one of the *Mycoplasma bovis* biotypes identified in step (a); and
(c) administering to the bovine animals the vaccine of step (b),
whereby the incidence of mastitis in the bovine animals is reduced.

54. (new) The method of claim 53 where the sample is milk.

55. (new) The method of claim 53 where step (a) comprises genetic analysis of DNA or RNA from the *Mycoplasma bovis* biotypes.

56. (new) The method of claim 55 where the genetic analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

57. (new) The method of claim 56 where the genetic analysis is PCR fingerprinting.

Remarks

This application was filed to pursue non-elected subject matter that was subject to a restriction requirement during prosecution of the parent application, U.S. Patent Application Serial No. 09/708,352. See the Office Action dated August 24, 2001, where claims 13-17 and 20, directed to methods of immunizing cattle against disease caused by *Mycoplasma bovis* (Group II) were subject to restriction. The Applicants subsequently chose to prosecute the claims of Group I. This Preliminary Amendment presents a new set of claims directed to subject matter of Group II.

New claims 21-57 are supported in the specification as follows:

New claim 21

Support is found in the specification at page 18, line 24 to page 20, line 17 and at page 20, line 20 to page 21, line 25 (see in particular page 21, lines 11-12).

New claim 22

Support is found in the specification at page 18, line 24 to page 19, line 31.

New claim 23

Support is found in the specification at page 23, lines 1-2.

New claim 24

Support is found in the specification at page 8, lines 7-8.

New claim 25

Support is found in the specification at page 8, lines 16-26 and page 11, lines 3-4. A water-oil-water emulsion is disclosed at Example 2, part D ("Adjuvanting and Formulation of Vaccine"), page 17, lines 17-19, where in step 7 it is disclosed that an oil adjuvant is

added to the inactivated *M. bovis* so as to produce a vaccine with 4% to 12% oil. One skilled in the art would understand that such a low amount of oil in the vaccine would not be enough to completely surround the aqueous phase of the vaccine and thus one skilled in the art would understand this passage to be a disclosure of an water-oil-water emulsion.

New claim 26

Support is found in the specification at page 10, line 22.

New claim 27

Support is found in the specification at page 9, lines 3-4.

New claim 28

Support is found in the specification at page 9, lines 4-6.

New claim 29

Support is found in the specification at page 4, lines 10-19.

New claim 30

Support is found in the specification at page 4, lines 13-17.

New claim 31

Support is found in the specification at page 4, lines 17-19 and page 16, lines 22-28.

New claim 32

Support is found in the specification at page 5, lines 23-25 and page 9, lines 1-2.

New claim 33

Support is found in the specification at page 5, lines 22-23.

New claim 34

Support is found in the specification at page 7, lines 12-13.

New claim 35

Support is found in the specification at page 10, line 5 and page 10, line 8.

New claim 36

Support is found in the specification at page 10, line 12.

New claim 37

Support is found in the specification at page 10, line 17.

New claim 38

Support is found in the specification at page 9, lines 20-22.

New claim 39

Support is found in the specification at page 5, lines 25-27.

New claim 40

Support is found in the specification at page 7, line 31.

New claim 41

Support is found in the specification at page 8, lines 1-5.

New claim 42

Support is found in the specification at page 5, lines 12-13, Figures 1 and 2.

New claim 43

Support is found in the specification at page 12, lines 6-28; Figures 1 and 2; and page 5, line 13.

New claim 44

Support is found in the specification at page 12, line 4 to page 14, line 13.

New claim 45

Support is found in the specification at page 12, line 10.

New claim 46

Support is found in the specification at page 12, lines 13-14.

New claim 47

Support is found in the specification at page 12, lines 15-28; and Figures 1 and 2

New claim 48

Support is found in the specification at page 7, lines 2-4.

New claim 49

Support is found in the specification at page 10, lines 23-27.

New claim 50

Support is found in the specification at page 7, lines 4-7.

New claim 51

Support is found in the specification at page 7, lines 4-7.

New claim 52

Support is found in the specification at page 9, line 31 to page 10, line 1.

New claim 53

Support is found in the specification at page 14, lines 21-31; page 15, line 20 to page 16, line 19; page 18, line 24 to page 19, line 15.

New claim 54

Support is found in the specification at page 14, lines 21-31.

New claim 55

Support is found in the specification at page 5, lines 12-13; and Figures 1 and 2.

New claim 56

Support is found in the specification at page 12, lines 6-28; Figures 1 and 2; and page 5, line 13; Figures 1 and 2.

New claim 57

Support is found in the specification at page 12, line 4 to page 14, line 13; Figures 1 and 2.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: DEC. 1, 2003

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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
TRANSMITTAL LETTER AND REQUEST FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. 1.136 (a)		Docket Number **12780/102**	
Application Number **10/726,029**	Filing Date **December 2, 2003**	Examiner **Ford**	Art Unit **1645**
Invention Title **VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE**		Inventors **Joan D. LEONARD et al.**	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandra, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: December 14, 2006

Signature: Joseph A. Hardy

Sir:

1. Transmitted herewith for filing is a response to the Office Action mailed June 15, 2006 for the above-identified application.

2. Applicant hereby requests a **three-month extension of time** to respond to the Office Action mailed June 15, 2006 which set a three-month period for response ending on September 15, 2006. The three-month extended period for response expires on December 15, 2006. Please charge the **$510.00** extension fee and any additional fees to the deposit account of Kenyon & Kenyon LLP, deposit account number 11-0600. A duplicate of this transmittal letter is enclosed for that purpose.

Respectfully submitted,
KENYON & KENYON LLP

Date: December 14, 2006

Joseph A. Coppola
Reg. No. 38,413

One Broadway
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Telephone: (212) 425-7000
Facsimile: (212)425-5288

A. ney Docket No. 12780/102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Joan D. LEONARD et al.
SERIAL NO.	:	10/726,029
FILING DATE	:	December 2, 2003
FOR	:	VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE
EXAMINER	:	Ford
GROUP ART UNIT:		1645

MAIL STOP AMENDMENT
COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: December 14, 2006

Signature: Gabriel Hardy
JOSEPHINE HARDY

AMENDMENT

Sir:

In response to the Office Action dated June 15, 2006, please consider the following amendments and remarks. Enclosed herewith is a Petition for the Extension of Time.

CLAIM AMENDMENTS:

This listing of claims will replace all prior versions and listings of claims in the application:

1-20. (canceled)

21. (currently amended) A method of immunizing bovine animals comprising administering to bovine animals at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

22. (previously presented) The method of claim 21 comprising administering at least one inactivated *Mycoplasma bovis* biotype to a plurality of cows in a herd of cows and determining that the incidence of mastitis caused by *Mycoplasma bovis* in the herd before administering was greater than the incidence of mastitis caused by *Mycoplasma bovis* in the herd after administering.

23. (previously presented) The method of claim 22 comprising administering at least one inactivated *Mycoplasma bovis* biotype to at least about 50% of the herd.

24. (previously presented) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with an adjuvant.

25. (currently amended) The method of claim 24 where the adjuvant is an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; incomplete Freund's adjuvant; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer

of amino acids; saponin; carrageenan; ~~REGRESSIN®;~~ N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; paraffin oil; or muramyl dipeptide.

26. (previously presented) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered together with a pharmaceutically acceptable excipient.

27. (previously presented) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered orally, intranasally, intratracheally, intramuscularly, intramammarily, subcutaneously, intravenously, or intradermally.

28. (previously presented) The method of claim 21 where the inactivated or attenuated *Mycoplasma bovis* biotype is administered by injection, inhalation, ingestion, or infusion.

29. (previously presented) The method of claim 21 where the *Mycoplasma bovis* biotype has been inactivated.

30. (previously presented) The method of claim 29 where the *Mycoplasma bovis* biotype has been inactivated by treatment with: formalin, azide, freeze-thawing, sonication, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal, or binary ethyleneimine.

31. (previously presented) The method of claim 30 where the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone.

32. (previously presented) The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes are administered.

33. (previously presented) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are selected from the group consisting of Biotype A, Biotype B, and Biotype C.

34. (previously presented) The method of claim 32 where at least 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

35. (previously presented) The method of claim 32 where approximately 10^8 cell equivalents of each *Mycoplasma bovis* biotype are administered.

36. (previously presented) The method of claim 32 where at least approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

37. (previously presented) The method of claim 32 where approximately 10^5 cell equivalents of each *Mycoplasma bovis* biotype are administered.

38. (previously presented) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are administered separately.

39. (previously presented) The method of claim 21 where at least two inactivated *Mycoplasma bovis* biotypes and an antigen derived from another pathogen are administered.

40. (previously presented) The method of claim 39 where the antigen from another pathogen is from an attenuated or inactivated virus.

41. (previously presented) The method of claim 39 where the antigen from another pathogen is selected from the group consisting of antigens from *Staphylococcus aureus, Pasteurella hemolytica, Pasteurella multocida, Hemophilus somnus*, Bovine Respiratory Syncytial Virus, *E. coli*, and the organism causing Infectious Bovine Rhinotrachial Disease.

42. (previously presented) The method of claim 32 where the at least two inactivated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

43. (previously presented) The method of claim 42 where the analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

44. (previously presented) The method of claim 43 where the analysis is by PCR fingerprinting.

45. (previously presented) The method of claim 44 where the PCR fingerprinting uses arbitrarily chosen primers.

46. (previously presented) The method of claim 44 where the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

47. (canceled)

48. (previously presented) The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are administered in a specific ratio.

49. (previously presented) The method of claim 32 where the at least two *Mycoplasma bovis* biotypes are grown separately as pure cultures, inactivated, and combined together in equal amounts before being administered to the animal.

50. (currently amended) A method for immunizing bovine animals comprising administering to bovine animals an antigenic component from at least one inactivated or attenuated *Mycoplasma bovis* biotype, whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

51. (previously presented) The method of claim 50 where antigenic components from at least two *Mycoplasma bovis* biotypes are administered.

52. (previously presented) The method of claim 21 where the administering results in greater milk production, greater weight gain, or less clinical disease in the bovine animal.

53. (currently amended) A method of immunizing bovine animals comprising:
(a) testing samples from bovine animals for the presence of *Mycoplasma bovis* biotypes, thereby identifying specific *Mycoplasma bovis* biotypes in the samples;
(b) preparing a vaccine by inactivating at least 10^5 cell equivalents of at least one of the *Mycoplasma bovis* biotypes identified in step (a); and
(c) administering to the bovine animals the vaccine of step (b),
whereby the bovine animals are immunized so that the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering.

54. (previously presented) The method of claim 53 where the sample is milk.

55. (previously presented) The method of claim 53 where step (a) comprises genetic analysis of DNA or RNA from the *Mycoplasma bovis* biotypes.

56. (previously presented) The method of claim 55 where the genetic analysis is PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

57. (previously presented) The method of claim 56 where the genetic analysis is PCR fingerprinting.

58. (previously presented) The method of claim 21 whereby the administering does not cause unfavorable reactions.

59. (previously presented) The method of claim 32 whereby the administering does not cause unfavorable reactions.

60. (previously presented) The method of claim 29 whereby the at least one inactivated *Mycoplasma bovis* biotype has not been inactivated with formalin.

61. (previously presented) The method of claim 32 whereby the at least two inactivated *Mycoplasma bovis* biotypes have not been inactivated with formalin.

Remarks

Claims 21-46 and 48-61 are pending.

The rejection under 35 U.S.C. §102(b)

The rejection of claims 21-30, 50, and 52 as being anticipated by Boothby et al., 1986, Cornell Vet. 76:188-197 (Boothby I) was maintained.

The Applicants respectfully traverse this rejection since it depends on an unreasonable interpretation of the term "incidence." The Office Action states that this rejection is based on the disclosure of Boothby I at page 194. See the Office Action, page 4, lines 14-18:

> Boothby I teaches that at weeks 12-15, 16 quarters or (4 cows) were infected with *Mycoplasma* (page 194) and at weeks 15.5 and 19.5 all 16 quarters (4 cows) were culture-negative for M. bovis (page 194). Therefore, the prior art teaches the claimed invention based on Applicant's definition of the term "incidence."

This portion of Boothby I refers to infected quarters in which the infection resolves itself over time. This can be seen by examining the entire two paragraphs which the Office Action refers to:

> During the acute phase of the experimental *M. bovis* infection (weeks 12-15), all 16 challenged quarters from vaccinated and control groups, and most unchallenged quarters from both the control (7 of 8) and the vaccinated (6 of 8) groups developed an *M. bovis* infection. Mean numbers of organisms were almost 10^9 cfu/ml in challenged quarters but were less than 10^5 cfu/ml in unchallenged quarters. By week 14, all unchallenged quarters on the vaccinated group (except for 10^1 cfu/ml from one quarter at week 15) had resolved the infection, while about 50% of similar quarters on the control cohort remained infected. [underscoring added]

> During the post-acute period (weeks 15.5-19.5) all of the 16 quarters (challenged and unchallenged) from the 4 vaccinated cows became culture-negative for mycoplasmas. Among the control cohort, about 25% of unchallenged quarters and about half of the challenged quarters remained infected with *M. bovis*.

It is clear that the numbers Boothby I cites and that are referred to in the Office Action pertain to differences in duration of infection, i.e., the decline in number of infected quarters over time which results from the resolution of infections in already infected quarters. Boothby I itself states this. See page 194, first two sentences, under the heading "Discussion," i.e., the sentences immediately preceding the paragraphs quoted above:

> There was little or no difference in number of infected quarters on vaccinated and control cows. Differences did, however, emerge with respect to duration of infection and the inflammatory responses. [underscoring added]

See also page 190, 4th paragraph:

> No difference was noted between unchallenged quarters which had been vaccinated and those which had both been vaccinated nor between vaccinated and unvaccinated challenged quarters for the variables under consideration (mycoplasmal infection and cellular inflammatory response).

Although Boothby I disclosed administering killed *M. bovis*, Boothby I did not disclose that the number or percentage of cows showing clinical symptoms of mastitis was less after such administering than before such administering, as required by the presently amended claims. The cows in Boothby I were free of clinical symptoms of mastitis before Boothby I administered killed *M. bovis* to them. See the sentence bridging pages 189-190: "During this time [i.e., before the experiments began] the cows showed no clinical mastitis ..." Boothby I administered killed *M. bovis* to the cows at weeks 0 to 8 of the experiment. See page 190, 6th paragraph: "The four vaccinated cows were inoculated with 2 ml of antigen ... at 3 locations subcutaneously at weeks 0, 2, 4 and with 3 mls ... by intramammary infusion at weeks 6 and 8." At week 12, Boothby I infected the cows with *M. bovis*. See page 190, 2nd paragraph: "Experimental intramammary challenge exposure was performed one week after all the cows had calved (week 12)."

Thus, before Boothby I administered killed *M. bovis*, the number and percentage of cows showing clinical symptoms of mastitis was zero. Accordingly, the number and percentage of cows showing clinical symptoms of mastitis cannot have been less after, as

opposed to before, Boothby I administered killed *M. bovis* because Boothby I began with zero cows showing clinical symptoms of mastitis and there could not have been less than zero cows showing clinical symptoms of mastitis after Boothby I administered killed *M. bovis*.

The Office Action is interpreting a reduction in the term "incidence" as including a reduction in the duration of infections in cows that are already infected with *M. bovis*. This is an unreasonable interpretation because it is contrary to how the specification refers to a reduction in "incidence" and it is contrary to how the term "incidence" is used in art, as shown by the evidence of record.

The specification

The specification consistently uses a reduction in "incidence" to refer to a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination. The specification does not use a reduction in "incidence" to refer to the resolution of infection in cows that are already infected with *M. bovis*. See page 19, lines 17-31:

> Comparative results were used to measure efficacy of the vaccine. Samples taken from all animals presenting with clinical mastitis were cultured by an independent laboratory to monitor the absence or presence of *Mycoplasma bovis* infection of the mammary gland. Field evaluations were made by comparing clinical incidence of mastitis caused by *Mycoplasma bovis* following herd vaccination to the base line herd incidence prior to vaccination. Results were as follows:
>
> Pre Vaccination Base Line Incidence:
> 155 confirmed positive clinical Mycoplasma bovis infections
>
> Post Vaccination Herd Incidence:
> 1st year following vaccination:
> 24 confirmed positive clinical Mycoplasma bovis infections
> 2nd year following vaccination:
> 1 confirmed positive clinical *Mycoplasma bovis* infection.

This passage describes the results of a field trial of the claimed vaccine. The vaccine was evaluated by counting the number of cows with clinical mastitis before and after vaccination. The numbers of cows so obtained were referred to by the term "incidence."

This use of the term "incidence" is also seen in the specification at page 21, lines 11-15:

> Following vaccination of a significant portion of the herd at Site 1 and Site 2, the incidence of mycoplasma was greatly reduced. From January 1, 2000 to July 18, 2000, there were only 10 animals reported positive for *Mycoplasma bovis* at each site. This reduction in the incidence of *Mycoplasma* positive mastitis cows was regarded as a significant reduction by the operators of Sites 1 and 2.

See also the specification at page 22, line 28 to page 23, line 1:

> Following the initiation of the vaccination regime for the herd in February, 2000, a veterinarian monitored the herd for the incidence of *M bovis*. The dairy reported in September 2000 that there were no confirmed cases of *Mycoplasma* in vaccinated animals, despite the continued challenge from the presence of confirmed, infected nonvaccinated animals.

The evidence of record

The Medical Dictionary Online, available at http://www.online-medical-dictionary.org/omd.asp?q=incidence[1] states that "incidence" is "The number of new cases of a given disease during a given period in a specified population." The portion of Boothby I cited in the Office Action does not represent a description of a reduction in "incidence" of infections, as that term is defined in The Medical Dictionary Online.

Epidemiology, Gordis, Third Ed., 2004, Elsevier Saunders, Philadelphia, PA. (Gordis) uses the term "incidence" in a way that is inconsistent with the interpretation of the

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[1] A copy of the entry for "incidence" from The Medical Dictionary Online was submitted as Exhibit A accompanying the Amendment filed March 14, 2006.

Office Action. See page 33, left column: "The *incidence* of a disease is defined as the number of new cases of a disease that occur during a specified period of time in a population at risk for developing the disease." [italics in original] See also page 33, paragraph bridging left and right columns: "Incidence is a measure of events – the disease is identified in a person who develops the disease and did not have the disease previously." [underscoring added] The Applicants note that Gordis's understanding that the term "incidence" is only applied when the person "did not have the disease previously" rules out the application of the term "incidence" to the situation described in Boothby I.

The Office Action refers to no evidence where the term "incidence" is applied to the situation described in Boothby I. In view of this, the Applicants believe that this rejection is in error and the present claims are not anticipated by Boothby I.

Nevertheless, in the interests of expediting prosecution, claim 21 has been amended to recite that "the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering."[2] This amendment makes it even clearer that the claims are not anticipated by Boothby I since Boothby I does not disclose a reduction in infections after, as compared to before, Boothby I administered killed *Mycoplasma bovis* to the cows.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §103(a)

The rejection of claims 21-31, 50 and 52 as being obvious over Boothby I in view of Koski et al., 1976, J. Biological Standardization 4:151-154 (Koski) was maintained.

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[2] Claims 50 and 53 have been similarly amended.

As discussed above, Boothby I does not disclose the limitation of claims 21-30, 50, and 52 that "the incidence of mastitis in the bovine animals is reduced." Boothby I also does not suggest this limitation, or teach how to obtain this limitation with a reasonable expectation of success. Therefore, Boothby I does not make obvious claims 21-31, 50, and 52.

Adding Koski to Boothby I does not cure the defects of Boothby I. There is no mention of mastitis in Koski. Accordingly, Koski does not disclose or suggest the limitation that "the incidence of mastitis in the bovine animals is reduced." Therefore, the combination of Boothby I and Koski does not make obvious claims 21-31, 50, and 52.

Claim 31 depends from claim 30 and adds the limitation that "the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone." Koski was cited in the Office Action for the proposition that it was known in the art to inactivate mycoplasmas with β-propiolactone. Therefore, it supposedly would have been obvious to combine Koski with Boothby I in order to arrive at the inactivated *Mycoplasma bovis* vaccine used in the methods of the present invention.

However, it would not have been obvious to combine Koski with Boothby I because:

- Koski's disclosure is directed to mycoplasmas other than *Mycoplasma bovis*; and
- Koski taught the inactivation of mycoplasmas for reasons other than for the production of vaccines against mycoplasma-caused diseases.

Koski disclosed the inactivation of *Mycoplasma gallisepticum, Mycoplasma canis,* and *Acholeplasma laidlawii.* Koski did not disclose the inactivation of *Mycoplasma bovis.*

Koski's purpose in inactivating mycoplasma was to reduce the level of mycoplasma contamination in vaccines that were directed to other microorganisms, i.e., microorganisms

other than mycoplasma. See page 151: "Because the U.S. Department of Agriculture ... requires a test for mycoplasma in vaccines intended for veterinary use it was of interest to establish whether these agents which are used to inactivate vaccines would also inactivate contaminating mycoplasmas."

Since Koski is directed to reducing the level of mycoplasmas in vaccines against microorganisms other than mycoplasmas, one of ordinary skill in the art would not combine Koski with Boothby I. And even if such a combination were made, the most that could be arrived at would be the inactivation of *Mycoplasma bovis* contaminants in vaccines directed to other microorganisms. But all the present claims are directed to methods of immunizing bovine animals to reduce the incidence of mastitis caused by *Mycoplasma bovis* in those animals. Nothing in Koski provides a reasonable expectation that inactivating *Mycoplasma bovis* contaminants in vaccines directed to other microorganisms would result in a vaccine that could reduce the incidence of *Mycoplasma bovis*-caused mastitis. Koski does not even mention mastitis. One of ordinary skill in the art would have no reason to use any vaccines produced by the combination of Koski and Boothby I to immunize bovine animals against mastitis and would have no reasonable expectation that the use of any vaccines produced by the combination of Koski and Boothby I would be successful in reducing the incidence of mastitis.

Furthermore, additional considerations make it clear that claim 31 is not obvious. The Declaration of Dr. Joan D. Leonard, filed March 14, 2006, establishes the following relevant facts:

- The prior art disclosed many possible inactivating agents to choose from in addition to β-propiolactone (¶¶ 7-9 of the Declaration of Dr. Joan D. Leonard);

• There was no guidance in the prior art as to which inactivating agent might lead to the production of a vaccine that reduced the incidence of mastitis (¶ 10 of the Declaration of Dr. Joan D. Leonard); and

• It was surprising that inactivation with β-propiolactone would lead to a vaccine that reduced the incidence of mastitis (¶ 15 of the Declaration of Dr. Joan D. Leonard).

In view of this lack of guidance in the prior art with respect to the choice of β-propiolactone as inactivating agent and the surprising effect of β-propiolactone in producing a vaccine that reduced the incidence of mastitis, claim 31 must be viewed as being non-obvious over the prior art.

Furthermore, Dr. Leonard also explained that there was a long felt but unsatisfied need in the art for a *Mycoplasma bovis* vaccine that could reduce the incidence of mastitis. Dr. Leonard cites several publications[3] which indicate that such a vaccine would have been desirable but did not exist prior to the present invention. See the Declaration of Dr. Joan D. Leonard, at ¶¶ 11-14.

In addition to the above considerations, there are further publications that teach away from the present claims and thus indicate that the present claims are non-obvious. Boothby et al., 1986, Can. J. Vet. Res. 50:200-204 (Boothby II)[4], studied formaldehyde-killed *Mycoplasma bovis*. Boothby II tested whether killed *Mycoplasma bovis* would be effective as a vaccine against bovine mastitis and found that it was not.[5] Thus, Boothby II was

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[3] These publications cover a period from long before the present invention (1993) to soon after the present invention (2001).

[4] A copy of Boothby II was enclosed with the Information Disclosure Statement filed April 8, 2004.

[5] Despite their prior exposure to killed *Mycoplasma bovis*, the incidence of mastitis in the treated cows in Boothby II was not reduced (see page 202, middle column: "All experimentally challenged quarters became infected ...").

unsuccessful. Certainly it must be admitted that failure is a deterrent. The skilled person therefore would have been deterred by Boothby II from using inactivated *Mycoplasma bovis* to immunize bovine animals to reduce the incidence of mastitis and thus would have been deterred from seeking the solution provided by the Applicants.

Moreover, the treated animals in Boothby II showed significant and persistent reductions in the level of milk production. The control cows exhibited a smaller and more transient drop in milk production. See Figure 2 on page 202 for a comparison of treated and control cows. Thus, not only did the killed *Mycoplasma bovis* fail to reduce the incidence of mastitis in the treated cows, but it caused milk production to be even worse than it would have been had the cows not been treated. Since an important purpose for having dairy herds is to produce milk, the skilled person would certainly be deterred by a result that decreased the production of milk.[6] Given that Boothby II would have deterred the skilled person from immunizing bovine animals as claimed in two major respects – lack of efficacy and decrease in milk production – Boothby II must be seen as teaching away from the Applicants' invention. See, e.g., *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998): "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

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[6] This is recognized by Boothby II at page 200, right column, where it is stated: "If prophylactic vaccination is to be efficacious, it must have minimal effects on the health and productive capabilities of the cow."

Similarly, in Rosenbusch, 1998, 12th International Organisation of Mycoplasmology Conference, p. 185 (Rosenbusch)[7], the administration of inactivated *M. bovis* not only failed to confer protection against respiratory disease but was actually more detrimental than no administration at all. Rosenbusch reported that, following challenge: "A lung lesion score was combined with scores for febrile response and cultural reisolation of challenge to determine if a calf was affected or not. Only 1/5 of sham-vaccinated calves were affected, while 4/5 vaccinated calves were affected regardless of oil adjuvant used." Such failure to protect, combined with more harm to the vaccinated calves than to the sham-vaccinated calves, would have deterred the skilled person from attempting to make the present invention and thus teaches away from the present invention.

In contrast to Boothby II and Rosenbusch, the Applicants provided an invention which not only prevents disease but also is safe in that it preserves the health and well-being of the vaccinated animals. Most surprisingly, especially in view of prior art such as Boothby II and Rosenbusch, which taught that prior attempts to produce a *Mycoplasma bovis* vaccine led to products that caused unacceptably severe side effects, the vaccine of the present invention does not have a deleterious effect on the vaccinated animals. See the specification, at page 20, lines 1-2: "No injection reactions were observed. No inflammatory udder reactions were observed." See also the specification, at page 22, lines 20-22: "[T]he vaccinated animals performed well as measured by days to market and rate of gain, both important indicators of a calf s health and well-being." Although the specification does not explicitly mention milk production, the skilled person would understand that, since the specification does explicitly state that the vaccinated animals' "health and well-being" were not detrimentally effected by the vaccine, milk production would not have been compromised.

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[7] A copy of Rosenbusch was enclosed with the Information Disclosure Statement filed April 8, 2004.

The Applicants submit that the combination of high efficacy and no deleterious effect on the vaccinated animals' health and well-being is surprising in view of the prior art's failure to achieve this combination and leads to the conclusion that the present claims are non-obvious.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejection of claims 21-38, 42, 50, and 52 as being obvious over Boothby I and Koski and further in view of Poumarat et al., 1994, Veterinary Microbiology 40:305-321 (Poumarat) was maintained.

As discussed above, the combination of Boothby I and Koski does not make obvious claims 21-38, 42, 50, and 52 since the combination of Boothby I and Koski does not disclose or suggest the limitation that "the incidence of mastitis in the bovine animals is reduced." Poumarat also does not disclose or suggest this limitation. Thus, adding Poumarat to the combination of Boothby I and Koski does not make obvious claims 21-38, 42, 50, and 52.

In addition, claims 32-38 and 42 contain the limitation that at least two inactivated *Mycoplasma bovis* biotypes are administered. Poumarat was cited in the Office Action for the proposition that it would have been obvious to administer at least two inactivated *Mycoplasma bovis* biotypes. The Office Action's reasoning in support of this proposition is found at page 9, lines 16-20:

> One of ordinary skill in the art would interpret the teachings of Poumarat et al differently than Applicants' interpretation because Poumarat et al teach that there is a marked intraspecies genomic heterogeneity among isolates of *Mycoplasma bovis* collected from different geographic origins and that antigenic variability must be taken into account in developing diagnostic and vaccination strategies.

Even assuming, *arguendo*, that Poumarat teaches that "there is a marked intraspecies genomic heterogeneity among isolates of *Mycoplasma bovis*" and that Poumarat teaches that "antigenic variability must be taken into account," Poumarat nevertheless teaches away because Poumarat teaches that this "marked intraspecies genomic heterogeneity" does not translate into "antigenic variability" such that it would be beneficial to include more than one type of *Mycoplasma bovis* in a vaccine. In this way, Poumarat teaches away from the administration of at least two inactivated *Mycoplasma bovis* biotypes.

Poumarat divided *Mycoplasma bovis* isolates into 13 different "genomic groups." Poumarat then looked at the antigenic variability between and among these genomic groups. Although Poumarat found much antigenic variability, this variability did not correlate with membership in any particular genomic group. In other words, the same amount of antigenic variability could be found within groups as between groups. See page 318, 2nd paragraph:

> Antigenic profiles of the *M. bovis* strains obtained by immunoblotting with J008 calf serum differed markedly one from the other, the heterogeneity being equally great among strains belonging to the same genomic group and those coming from different genomic groups. There appeared to be no relation between the genomic variability of *M. bovis* and the antigenic variability ...

Because Poumarat teaches that antigenic variability is as great within *Mycoplasma bovis* groups as across *Mycoplasma bovis* groups, Poumarat teaches that there would be no gain in antigenic variability from including more than one type of *Mycoplasma bovis* in a vaccine. That is, there would be no point in having more than one type of *Mycoplasma bovis* in a vaccine. Poumarat thus discourages one of ordinary skill in the art from including more than one biotype in a vaccine and therefore Poumarat teaches away from claims 32-38 and 42.

Poumarat's teaching away is especially pertinent in connection with claim 42. This claim requires that the at least two biotypes be genetically different, as judged by analysis of DNA or RNA. Poumarat teaches that such genetic differences are irrelevant with respect

to antigenicity since Poumarat teaches that there appears to be "no relation between the genomic variability of *M. bovis* and the antigenic variability." One of ordinary skill in the art would interpret this as a teaching that nothing is to be gained from including biotypes that are genetically different in a vaccine and thus would be led away from the invention of claim 42.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 21-38, 42-45, and 48-57 were rejected as being obvious over Boothby I, Koski, and Poumarat, and further in view of Rawadi, 1998, Methods in Molecular Biology 104:179-187 (Rawadi).

As discussed above, the combination of Boothby I, Koski, and Poumarat does not make obvious claims 21-38, 42-45, and 48-57 because the combination of Boothby I, Koski, and Poumarat does not disclose or suggest the limitations of those claims with respect to incidence of mastitis and/or administration of at least two inactivated *Mycoplasma bovis* biotypes. Rawadi does not disclose or suggest these limitations either. Therefore, adding Rawadi to the combination of Boothby I, Koski, and Poumarat does not make obvious claims 21-38, 42-45, and 48-57.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 21-39, 41-45, and 48-57 were rejected as being obvious over Boothby I, Koski, Poumarat, and Rawadi, and further in view of U.S. Patent No. 4,425,330 (Norcross).

As discussed above, the combination of Boothby I, Koski, Poumarat, and Rawadi does not make obvious claims 21-39, 41-45, and 48-57 because the combination of Boothby I, Koski, and Poumarat does not disclose or suggest the limitations of those claims with respect to incidence of mastitis and/or administration of at least two inactivated *Mycoplasma bovis* biotypes. Norcross does not disclose or suggest these limitations either. Therefore, adding Norcross to the combination of Boothby I, Koski, Poumarat, and Rawadi does not make obvious claims 21-39, 41-45, and 48-57.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 21-45, and 48-57 were rejected as being obvious over Boothby I, Koski, Poumarat, and Rawadi, and further in view of Straub, 1991, Comp. Immunol. Microbiol. Infect. Dis. 14:175-186 (Straub).

As discussed above, the combination of Boothby I, Koski, Poumarat, and Rawadi does not make obvious claims 21-45, and 48-57 because the combination of Boothby I, Koski, and Poumarat does not disclose or suggest the limitations of those claims with respect to incidence of mastitis and/or administration of at least two inactivated *Mycoplasma bovis* biotypes. Straub does not disclose or suggest these limitations either. Therefore, adding Straub to the combination of Boothby I, Koski, Poumarat, and Rawadi does not make obvious claims 21-45, and 48-57.

In view of the above, it is respectfully requested that this rejection be withdrawn.

<u>The rejections under 35 U.S.C. §112</u>

Claim 25 was rejected as being indefinite because of the recitation of "REGRESSIN®."

Claim 25 has been amended to delete this recitation. Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 21-46 and 48-61 were rejected as being indefinite because of the recitation of the phrase "whereby the incidence of mastitis in the bovina animals is reduced." According to the Office Action, this phrase is indefinite because "there is no indication that the bovine animals of the preamble have mastitis."

The Applicants respectfully traverse this rejection. A claim is indefinite only if one skilled in the art would not understand what is claimed when the claim is read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986) ("A decision on whether a claim is invalid under § 112, 2d ¶, requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."). Method claims are not indefinite if one skilled in the art can determine whether a particular process is within the scope of the claims. *Application of Mercier*, 185 USPQ 774, 780, 515 F. 2d 1161, 1168 (CCPA 1975): "[I]f one can determine whether a particular catalytic process for splitting acetals and hemi-acetals is or is not within the scope of a claim, the claim fulfills its purpose as a definition."

One skilled in the art would understand from the specification, in particular the working examples at pages 18-23, that the claims are directed to methods of immunizing cows where the number or percentage of cows showing clinical symptoms of mastitis is reduced after immunization as compared to before immunization. Furthermore, one skilled

in the art would be able to determine whether a particular process is or is not within the scope of the present claims by determining whether the number or percentage of cows showing clinical symptoms of mastitis is reduced after immunization as compared to before immunization. There is no need to specify that the cows have mastitis in order for the specification to be so understood or to determine if a particular process falls within the scope of the present claims. This rejection appears to be based on the view that the claims are directed merely to methods of reducing the duration of infections. As discussed above in connection with the rejection under 35 U.S.C. §102(b), this view is untenable. Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 21-46 and 48-61 were rejected as being indefinite because, according to the Office Action the specification fails to use the term "incidence" as it is used in Epidemiology, Gordis, Third Ed., 2004, Elsevier Saunders, Philadelphia, PA. (Gordis).

The Applicants respectfully traverse this rejection. The Applicants respectfully submit that the relevant issue is not whether the specification uses the term "incidence" precisely as it is used in a particular publication such as Gordis. Instead, the relevant issue is whether the use of the term "incidence" in the claims is such that one of ordinary skill in the art would understand what the claims cover, when the term "incidence" is read in light of the specification. As discussed above in connection with the rejection under 35 U.S.C. §102(b), the specification uses a reduction in "incidence" to mean a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination. Thus, reading the claims in light of the specification would lead one of ordinary skill in the art to understand exactly what is being claimed. In view of this, the claims are definite.

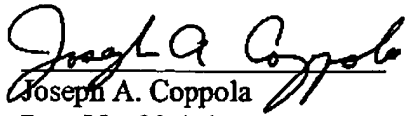
In view of the above, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for September 15, 2006. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response. Please charge any corresponding fees for the Petition to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: December 14, 2006



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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@kenyon.com

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/726,029	Applicant(s) LEONARD ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *23 August 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *21-46 and 48-61*.
   Claim(s) withdrawn from consideration: *NONE*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see advisory attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: Advisory attachment.

Advisory Attachment

1. This Office Action is responsive to Applicant's response filed August 23, 2007.

Rejections Maintained

The rejection is reiterated below:

2. The rejection under 35 U.S.C. 112, first paragraph (new matter) is maintained for claims 21-46 and 48-61 for the reasons set forth on pages 3-4, paragraph 3 of the Final Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-46 and 48-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* The amendment filed December 18, 2006 introduces new matter into the claims.

The claims have been amended to recite, "...such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering...". 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant's amendment introduces "new matter" that is not supported by the original disclosure. The specification fails to show the claim limitation "a reduction in the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering". Applicant has failed to direct the Examiner as to where in the instant specification the support for this amendment is specifically shown or implied. In Applicant's response and marks (filed December 18, 2006) Applicant refers to incidence as a reduction in the number or percentage of cows showing clinical symptoms of mastitis after vaccination as compared to before vaccination. Applicant points to page 19, lines 17-31 of the specification to support this conclusion. The results on page 19 measure efficacy of the vaccine. There is no mention of symptoms of disease or the percentage of symptoms reduced. The

Examiner has reviewed the instant specification and has failed to find the support for the amendment. Applicant is required to cancel the new matter in the reply to this Office Action.

Applicant's Arguments

Applicant urges that a written description need not describe the subject matter claimed in the same words as are used in the claims. Applicant urges that the instant specification provides written description for the amendment filed December 14, 2006 which amended the claims to recite the phrase "such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after administering than before administering".

Applicant urges that the specification describes administration of the recited vaccine to bovine animals followed by a description of such beneficial effects of the vaccine as reduction in levels of infection, lack of clinical mastitis event and lack of confirmed cases of mastitis in vaccinated animals. Applicant urges that the instant specification states that the vaccine decreases the effect of *M. bovis* infections on milk production, weight gains and animal health. Applicant refers to pages 19-23 of the instant specification that discloses field evaluations of the bovine animals. Applicant asserts that they are in possession of the claimed subject matter and the specification supports the phrase " such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after administering than before administering".

Examiner's Response to Applicant

Applicant's arguments filed August 23, 2007 have been fully considered but they are not persuasive.

It is the Examiner's position that the amendment filed December 14, 2006 introduces new matter. The instant specification merely shows that after administration of the vaccine used in the claimed method bovine positive for *Mycoplasma bovis* infections had decreased (page 19 of the specification). The instant specification discloses that milk samples were taken from cows and screened (page 20 of the specification). Page 22 of the instant specification disclose that it is believed that vaccinated animals performed well as measured by days to market and rate of gain. However, there is no disclosure in the instant specification that shows that a reduced number or percentage of bovine animals *show less clinical symptoms of mastitis* after administration of the vaccine than before administration of the vaccine. The instant specification merely discloses *a reduction of animals that do not have mastitis*. In other words, the specification discloses the number or percentage of animals protected from disease after they have been administered the vaccine used in the claimed method. The specification is silent to the number animals that *have symptoms of mastitis* but do not have mastitis. It should be noted that the phrase symptom of disease is defined as "an indication of an undesirable situation". However, as it relates to the claimed method, a symptom of mastitis (an indicator) can be reduced and the animals still have mastitis. This situation is also encompassed by the claimed invention. It should be remembered

that the claimed invention encompasses animals that have reduced symptoms as well as animals that do not have mastitis. The art recognizes symptoms of mastitis as animals with swollen utters or animals that are low milk producers to name a few. The specification does not provide data from animals that have the before mentioned symptoms of mastitis. Additionally, the instant specification does not teach or disclose what constitutes a level of reduction such that the incidence is reduced.

In view of all of the above, this rejection is maintained.

3. The rejection under 35 U.S.C. 112, first second is maintained for claims 21-46 and 48-61 for the reasons set forth on pages 4-5, paragraph 4 of the Final Office Action.

The rejection is reiterated below:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-46 and 48-61 recite "whereby the incidence of mastitis in the bovine animals is reduced such that the number or percentage of bovine animals that show clinical symptoms of mastitis is less after such administering than before such administering...". It is unclear as to what the Applicant is referring? What clinical symptoms are reduced? Does a reduction in clinical symptoms necessarily mean that incidence of mastitis is reduced? A symptom of a disease or disorder can be reduced and the subject still has the disease or disorder. The Clarification and/or correction is required.

Applicant's Arguments

Applicant urges that the word "symptom" is common and the meaning is well-understood. Applicant urges that the instant specification provides examples of symptoms of mastitis of animals after immunization as compared to before

immunization. Applicant assert that a reduction of clinical symptoms necessarily means that the incidence of mastitis reduced. Applicant urges that the Examiner's statement that a symptom of a disease or a disorder can be reduced and the subject still have the disease or disorder is not relevant to the claimed invention.

Examiner's Response to Applicant's Arguments

It is the Examiner position that a reduction is symptoms does not necessarily mean that the incidence of mastitis is reduced. The Examiner agrees that the meaning of the term "symptom" is well understood. It should be remembered that a symptom of disease is defined as "an indication of an undesirable situation". However, as it relates to the claimed method, a symptom of mastitis (an indicator) can be reduced and the animals still have mastitis. This situation is also encompassed by the claimed invention. It is unclear as to what clinical symptoms Applicant is referring. It is also unclear as to what constitutes a level of reduction such that the incidence is reduced.

In view of all of the above, this rejection is maintained.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
September 11, 2007

NITA MINNIFIELD
PRIMARY EXAMINER
9-14-07